BMJ Open

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042315
Article Type:	Original research
Date Submitted by the Author:	01-Jul-2020
Complete List of Authors:	Morooka, Hikaru; Nagoya University Hospital, Nephrology Tanaka, Akihito; Nagoya University Hospital, Nephrology Inaguma , D.; Fujita Health University, Nephrology Maruyama, Shoichi; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Hikaru Morooka,[1] Akihito Tanaka,[1] Daijo Inaguma[2], Shoichi Maruyama[3]

[1]Division of Nephrology, Nagoya University Hospital, Nagoya, Japan

[2] Division of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan

[3]Division of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Corresponding author: Akihito Tanaka

Division of Nephrology,

Nagoya University Hospital

Tsurumaicho, 65, Showa Ward, Nagoya, Aichi, Japan

Tel: +81-52-741-2111

Fax: +81-52-744-2209

E-mail: tanaka17@med.nagoya-u.ac.jp

Word count: 2014.

ABSTRACT

Objectives: Patients with peripheral artery disease (PAD) are reported to have a poorer prognosis than those without PAD. PAD is sometimes found at dialysis initiation, but its influence on the prognosis in these patients has not been investigated. We aimed to compare the mortality between patients with PAD at the time of dialysis initiation and those without PAD.

Design: We undertook an observational prospective multicenter study of patients starting dialysis therapy. Data were collected on patients' sex, age, presence of PAD, medication, past medical history, and clinical and laboratory data.

Setting: Seventeen centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis.

Participants: A total of 1524 patients with chronic kidney disease who started dialysis from October 2011 to September 2013. The patients were followed up until March 2015.

Primary and secondary outcome measures: The primary outcome was defined as all-cause death. The secondary outcomes were defined as each cause of death**.**

Results: The study included 1030 men and 492 women with a mean age of 67.5 ± 13.1 years. Of these, 71 had PAD, and 1451 did not. After a median follow-up of 814.5 days, 33.8 % of the former and 17.0 % of the latter group had died by March 2015 ($p < 0.01$). After adjusting for confounding factors, PAD at dialysis initiation remained an independent risk factor for mortality ($p < 0.01$).

Conclusions: Patients with PAD at the time of dialysis initiation had a poorer prognosis than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Key words: Chronic kidney diseases; Dialysis; Mortality; Peripheral artery disease

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This observational prospective multicenter study analyzed data in patients at the beginning of dialysis and for a median follow-up of 814.5 days.
- Our study had a high follow-up rate (only two patients lost to follow-up) and a well-defined population with comprehensive data at the start of dialysis.
- The number of patients with PAD at the initiation of dialysis was comparably small, and not all of them underwent peripheral angiography to confirm the diagnosis.

INTRODUCTION

The number of patients receiving dialysis therapy is increasing every year, and these patients have a high mortality risk from various causes, particularly cardiovascular diseases (CVD).[1, 2] End-stage kidney disease (ESKD) represents a considerable risk of atherosclerosis, and patients on dialysis tend to have further risk factors contributing to the rapid deterioration of CVD.[3] While CVD, including stroke, and coronary artery disease have been reported in more detail in patients on dialysis,[4-6] the problem of peripheral artery disease (PAD) in patients undergoing dialysis therapy has been less frequently addressed. With both aging and a growing number of diabetic patients on dialysis, the prevalence of PAD among these patients is likely to increase year by year.[7] PAD with distal lesions is more common in patients with ESKD, making the transarterial approach to the stenosis sometimes difficult.[8, 9] Furthermore, a vascular stenosis can promote peripheral ischemic skin ulcers or gangrene, leading to an intractable pathology. Thus, patients with PAD on dialysis therapy have a worse prognosis than those without PAD.[10] Consequently, there is an urgent need to clarify the relationships between PAD and mortality in patients on dialysis. Furthermore, to improve the prognosis of dialysis patients, it is crucial to understand the characteristics of those with high mortality risk.

The classic atherosclerosis risk factors, such as age, smoking, diabetes, hypertension, and hyperlipidemia, are common in patients with ESKD, but their chronic kidney disease (CKD) condition adds unique risk factors that promote PAD: chronic inflammation, hypoalbuminemia, and a pro-calcific state. PAD in ESKD patients markedly increases the possibility of myocardial ischemia and stroke, and is the main cause of limb loss and mortality, the rates of which are much higher than those in the general population.[10,11] Moreover, it has been pointed out that if patients with PAD develop critical limb ischemia,

their overall survival is worse than that of patients with malignant tumors.[12] Hence, when considering the prognosis of patients receiving dialysis, the presence of PAD is important.

There are few recent reports on PAD in patients with ESKD at the time of dialysis initiation. Several studies have investigated patients receiving maintenance dialysis. In these studies, descriptive data included the prognosis of "only maintenance dialysis" patients.[10, 13-15] According to them, PAD had an overall prevalence of 18.2 %, and the patient survival rate was 28.6 % during 8.8 years in the PAD group. Moreover, since these studies focused on patients on maintenance dialysis, they mainly addressed PAD that occurred during dialysis. However, renal function in patients with CKD may decrease during the treatment of PAD. At other times, PAD is found when investigating the cause of renal function deterioration or when screening patients for their eligibility for a renal transplant. PAD at the time of dialysis initiation is a complex and clinically relevant problem.

In the present study, we compared PAD and non-PAD patients who had started dialysis therapy in the Aichi prefecture to identify the mortality associated with PAD in ESKD patients at the time of initiation of dialysis therapy.

PATIENTS AND METHODS

Patient registration and data collection

Data from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis [14, 16] were used in this prospective multicenter study. Patients who started dialysis between October 2011 and September 2013 at 17 Japanese institutions were eligible for participation. This study was approved by the Ethics Committee of the Institutional Review Board in Nagoya University (Approval number 1335), and all patients provided written informed consent.

First, we screened all patients with ESKD who were initiated dialysis. Only patients who became stable and were discharged or transferred from the hospital were included. Patients who were not discharged and died in the hospital were excluded (Figure 1). Data regarding patients' demographics, medical history, comorbidities, medications, and laboratory data during the period of dialysis initiation were collected. PAD was clinically diagnosed based on symptoms, physical findings, and various examinations, but not all patients received angiography for diagnosis. We used the Fontaine classification for grading of severity.[17] The presence of PAD was defined as a Fontaine stage II or higher. Laboratory data were obtained immediately prior to the first dialysis session. Patients were followed until the end of March 2015.

Patient and public involvement

Patients were not involved at any stage of the research for this study.

Mortality

Patients were divided into one group with PAD and one group without PAD. The primary endpoint was all-cause mortality. Causes of death were recorded to the extent possible. The occurrence of death was investigated via survey slips sent to the dialysis facilities at the end of March 2015.

We compared the outcomes and hazard ratios (HRs) between the two groups.

Statistics

Baseline characteristics were presented descriptively and compared between the two groups using the Student's *t*-test or χ^2-test. Survival was presented graphically using the Kaplan-Meier method and analyzed using uni- and multivariate Cox regression. HRs were

calculated and presented graphically using forest plots. We used propensity score matching to account for differences in baseline characteristics between the two groups. The propensity score was calculated based on age, sex, presence of diabetes, medication (use of statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, and antiplatelets), laboratory data (levels of phosphorus, hemoglobin, and estimated glomerular filtration rate), and history of coronary artery disease.

P-values of < 0.05 were considered to be statistically significant. We used the R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/) for all statistical analysis. For the propensity score matching, the R-package MatchIt (1:3 matching with the nearest neighbor) was used.[18] Missing data were not complemented, however the characteristics we used for propensity score matching were not missing.

RESULTS

Baseline characteristics

Patients' baseline characteristics are shown in Table 1. The initial population included 1524 participants, of whom 1032 were men, and 492 were women. The mean age was 67.5 ± 13.1 years. Two patients were untraceable and lost to follow-up. Of the remaining 1522 patients, 71 (4.7%) had PAD, and 1451 did not. There were significant differences between patients with and without PAD with regard to comorbidities and drug use. Antiplatelet administration was significantly more frequent in those with PAD than in those without PAD. This may be because treatment for PAD includes antiplatelets. The prevalence of diabetes mellitus, coronary artery disease, and aortic dissection was significantly higher in those with than in those without PAD. Patients with PAD had significantly lower ejection fractions than patients without PAD. The use of both beta-blockers and statins was significantly higher in patients

with PAD than in those without PAD (beta-blockers: 34.0 % and 47.9 %, respectively, p = 0.024; statins: 39.4 % and 53.5 %, respectively, p = 0.024). The estimated glomerular filtration rate [19] was significantly higher in patients with PAD than in those without PAD (6.34 ± 1.83 mL/min per 1.7 m^2 and 5.40 ± 2.23 mL/min per 1.7m^2, respectively, p < 0.001). The median follow-up was 814.5 days (interquartile range 645-1037).

Mortality

During the follow-up period, 271 patients died from various causes, including cardiovascular events (102 patients, 37.6 %), infectious disease (56 patients, 20.7 %), cancer (45 patients, 16.6 %), and other causes. The PAD group had a significantly higher mortality rate of 33.8 % than the group without PAD with 17.0 % (p < 0.01; Table 1). Figure 2 shows the Kaplan-Meier plot for all-cause mortality in patients with and without PAD.

Table 1. Baseline and clinical characteristics and outcomes of patients starting dialysis (n = 1522)

	Patients without PAD(n = 1451)	**Patients with PAD (n= 71)**	**P value**
Female (%)	33.1	16.9	0.007
Age (years) (mean (SD))	67.4 (13.1)	69.9 (12.1)	0.106
Past history			
Diabetes (%)	50.2	67.6	0.006
CAD (%)	15.9	36.6	<0.001
PCI (%)	9.6	21.1	0.003
CABG (%)	3.8	14.1	<0.001
Aortic dissection (%)	5.0	15.5	<0.001
Admission of HF (%)	19.4	42.3	<0.001
Stroke (%)	9.1	7.0	0.704

Cause of CKD			0.294
Diabetes (%)	42.5	59.2	
Nephrosclerosis (%)	25.3	25.4	
CGN (%)	15.6	4.2	
Others, unknown (%)	4.3	4.2	
Vital data			
Pre-dialysis SBP (mmHg) (mean (SD))	151.1 (25.9)	151.7 (29.5)	0.843
Cardiac ultrasonography			
EF (%) (mean (SD))	60.9 (12.2)	55.8 (13.7)	0.001
Chest X-ray			
CTR (%) (mean (SD))	55.2 (7.2)	55.2 (7.1)	0.973
Administration			
ARB or ACEI (%)	60.6	56.3	0.554
BB (%)	34.0	47.9	0.024
Statin (%)	39.4	53.5	0.024
VDRA (%)	26.9	29.6	0.726
Antiplatelets (%)	28.9	56.3	<0.001
ESA (%)	85.8	87.3	0.861
Laboratory data			
WBC (/uL) (mean (SD))	6729.88 (3130.80)	7206.62 (3581.54)	0.214
Hb (g/dL) (mean (SD))	9.37 (1.55)	9.40 (1.45)	0.887
Plt (10 000/uL) (mean (SD))	18.24 (7.62)	18.17 (8.19)	0.943
Alb (g/dL) (mean (SD))	3.21 (0.59)	3.02 (0.62)	0.010
BUN (mg/dL) (mean (SD))	92.02 (30.69)	86.68 (24.84)	0.149

Cr (mg/dL) (mean (SD))	9.03 (3.24)	7.74 (2.22)	0.001
eGFR (mL/min/1.73m^2) (mean (SD))	5.40 (2.23)	6.34 (1.83)	0.001
Na (mEq/L) (mean (SD))	137.88 (4.41)	137.93 (3.91)	0.933
K (mEq/L) (mean (SD))	4.56 (0.84)	4.43 (0.81)	0.194
Adjusted Ca (mg/dL) (mean (SD))	8.59 (1.06)	9.06 (0.93)	<0.001
P (mg/dL) (mean (SD))	6.40 (1.89)	5.76 (1.56)	0.005
Mg (mg/dL) (mean (SD))	2.15 (0.49)	2.17 (0.44)	0.826
UA (mg/dL) (mean (SD))	8.80 (2.44)	8.64 (2.27)	0.582
LDL C (mg/dL) (mean (SD))	89.97 (34.25)	87.08 (37.14)	0.525
CRP (mg/dL) (mean (SD))	1.82 (4.14)	2.39 (4.68)	0.271
β2MG (ng/dL) (mean (SD))	19.32 (5.78)	17.33 (5.05)	0.027
TSAT (%) (mean (SD))	27.16 (16.60)	25.44 (17.95)	0.438
Ferritin (ng/dL) (mean (SD))	222.28 (1009.80)	226.65 (395.74)	0.972
Outcome			
Infection-related death (%)	3.4	8.5	0.062
CVD-related death (%)	6.6	11.6	0.167
All-cause death (%)	17.0	33.8	0.001

ACEI; angiotensin-converting enzyme inhibitor. Adjusted Ca; adjusted calcium. Alb; albumin. ARB; angiotensin receptor blocker. BB; beta blocker. BUN; blood urea nitrogen. β 2MG; beta-2 microglobulin. Ca; calcium. CABG; coronary artery bypass grafting. CAD; coronary artery disease. CGN; chronic glomerulonephritis. CKD; chronic kidney disease. Cr; creatinine. CRP; C-reactive protein. CTR; cardiothoracic ratio. CVD; cardiovascular disease. EF; ejection fraction. eGFR; estimated glomerular filtration rate. ESA; erythropoietin stimulating agent. Hb; hemoglobin. HF; heart failure. K; potassium. LDL-C; low-density

lipoprotein cholesterol. Mg; magnesium. Na; sodium. P; phosphate. PAD; peripheral arterial disease. PCI; percutaneous coronary intervention. Plt; platelet. SBP; systolic blood pressure. SD; standard deviation. TSAT; transferrin saturation. UA; uric acid. VDRA; Vitamin D receptor agonist. WBC; white blood cells.

Figure 3 shows the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group ($p = 0.048$). Figure 4 shows the Kaplan-Meier plot for infection-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group ($p = 0.011$). Figure 5 shows the forest plot for the HRs of PAD for all-cause death with adjustment for confounding factors. PAD was an independent risk factor for death (HR, 1.76; 95 % confidence interval, 1.15–2.69; $p < 0.01$).

Propensity score-matched comparison between patients with and without PAD

The baseline and clinical characteristics in Table 1 showed significant differences between patients in the group with and without PAD, suggesting that there was a possibility of bias. Table 2 shows the baseline characteristics of the propensity score-matched patients with (n=71) and without PAD (n=213).

Table 2. Baseline and clinical characteristics and outcomes of propensity-score matched patients starting dialysis (n = 284)

	Patients without PAD (n = 213)	Patients with PAD (n = 71)	P value
Female (%)	15.0	16.9	0.850
Age (years) (mean (SD))	69.1 (12.2)	69.9 (12.1)	0.607
Past history			

DM (%)	67.1	67.6	1.000
CAD (%)	40.4	36.6	0.674
PCI (%)	26.8	21.1	0.431
CABG (%)	9.9	14.1	0.442
Aortic dissection (%)	7.0	15.5	0.057
Admission of HF (%)	29.1	42.3	0.057
Stroke (%)	14.1	7.0	0.175
Cause of CKD			0.091
Diabetes (%)	58.7	59.2	
Nephrosclerosis (%)	25.4	25.4	
CGN (%)	8.5	4.2	
Others, unknown (%)	2.3	4.2	
Vital data			
Pre-dialysis SBP (mmHg) (mean (SD))	151.8 (28.3)	151.7 (29.5)	0.977
Cardiac ultrasonography			
EF (%) (mean (SD))	59.8 (13.8)	55.8 (13.7)	0.049
Chest X-ray			
CTR (%) (mean (SD))	55.3 (6.8)	55.2 (7.1)	0.885
Administration			
ARB or ACEI (%)	59.2	56.3	0.781
BB (%)	49.3	47.9	0.945
Statin (%)	58.7	53.5	0.533
VDRA (%)	27.2	29.6	0.819
Antiplatelets (%)	58.2	56.3	0.89
ESA (%)	89.7	87.3	0.742
Laboratory data			
WBC (/uL) (mean (SD))	6704.76 (2722.41)	7206.62 (3581.54)	0.217

Hb (g/dL) (mean (SD))	9.62 (1.43)	9.40 (1.45)	0.275
Plt (10 000/uL) (mean (SD))	17.90 (7.39)	18.17 (8.19)	0.796
Alb (g/dL) (mean (SD))	3.20 (0.60)	3.02 (0.62)	0.032
BUN (mg/dL) (mean (SD))	87.14 (27.58)	86.68 (24.84)	0.901
Cr (mg/dL) (mean (SD))	8.47 (2.82)	7.74 (2.22)	0.049
eGFR (mL/min/1.73m^2) (mean (SD))	6.05 (2.47)	6.34 (1.83)	0.368
Na (mEq/L) (mean (SD))	138.36 (4.56)	137.93 (3.91)	0.475
K (mEq/L) (mean (SD))	4.51 (0.83)	4.43 (0.81)	0.492
Adjusted Ca (mg/dL) (mean (SD))	8.71 (0.96)	9.06 (0.93)	0.007
P (mg/dL) (mean (SD))	5.96 (1.63)	5.76 (1.56)	0.372
Mg (mg/dL) (mean (SD))	2.22 (0.46)	2.17 (0.44)	0.497
UA (mg/dL) (mean (SD))	8.75 (2.49)	8.64 (2.27)	0.731
LDL C (mg/dL)(mean (SD))	87.07 (32.01)	87.08 (37.14)	0.999
CRP (mg/dL) (mean (SD))	1.61 (3.30)	2.39 (4.68)	0.137
β2MG (ug/dL) (mean (SD))	17.95 (5.04)	17.33 (5.05)	0.497
TSAT (%) (mean (SD))	25.41 (14.74)	25.44 (17.95)	0.992
Ferritin (ng/dL) (mean (SD))	171.44 (208.99)	226.65 (395.74)	0.153
Outcome			
Infection-related death (%)	3.8	8.5	0.206
CVD-related death (%)	8.2	11.6	0.537
All-cause death (%)	21.6	33.8	0.056

ACEI; angiotensin-converting enzyme inhibitor. Adjusted Ca; adjusted calcium. Alb; albumin. ARB; angiotensin receptor blocker. BB; beta blocker. BUN; blood urea nitrogen. β 2MG; beta-2 microglobulin. Ca; calcium. CABG; coronary artery bypass grafting. CAD; coronary artery disease. CGN; chronic glomerulonephritis. CKD; chronic kidney disease. Cr;

creatinine. CRP; C-reactive protein. CTR; cardiothoracic ratio. CVD; cardiovascular disease. EF; ejection fraction. eGFR; estimated glomerular filtration rate. ESA; erythropoietin stimulating agent. Hb; hemoglobin. HF; heart failure. K; potassium. LDL-C; low-density lipoprotein cholesterol. Mg; magnesium. Na; sodium. P; phosphate. PAD; peripheral arterial disease. PCI; percutaneous coronary intervention. Plt; platelet. SBP; systolic blood pressure. SD; standard deviation. TSAT; transferrin saturation. UA; uric acid. VDRA; Vitamin D receptor agonist. WBC; white blood cells.

Figure 6 shows the Kaplan-Meier plot for all-cause death in matched patients with and without PAD. Patients with PAD showed a significantly worse prognosis than those without. Figures 7 and 8 show the Kaplan-Meier plots for CVD-related and infection-related death, respectively, in matched patients with and without PAD with no significant differences between the groups. Figure 9 shows the forest plot for the HRs of matched patients with PAD for all-cause death with adjustment for confounding factors. PAD was an independent risk factor for death here, too (HR, 1.78; 95 % confidence interval, 1.07–2.95; p = 0.026).

DISCUSSION

Our study showed that patients with PAD at the time of dialysis initiation had a significantly higher mortality than patients without PAD. This higher risk should be considered in the treatment and monitoring of these patients.

A previous study suggested that the prevalence of PAD in patients with ESKD reached almost 20 %.[15] In our cohort, the prevalence of PAD was much lower, most likely because our patients started dialysis, whereas the patients in the literature where on maintenance dialysis. This might reflect a deterioration of peripheral atherosclerosis with longer duration of dialysis. Another study suggested that the chronic uremic state is

associated with systemic inflammation in dialysis patients, leading to hypoalbuminemia and an increased risk of PAD.[20] Hence, our results are remarkable because we showed the prevalence of PAD at the time of dialysis initiation, while past studies reported on PAD during maintenance dialysis. Furthermore, patients with PAD in our study more frequently had a decreased ejection fraction and decreased albumin and increased adjusted calcium levels than those without PAD, even after propensity score matching. We cannot exclude the possibility of other factors associated with PAD that were not corrected even after our propensity score matching. This implies that PAD is one symptom of a systemic atherosclerotic disease that affects not only the peripheral but also coronary arteries. When seeing patients with myocardial infarction or low cardiac systolic function, it is recommended to suspect that they have PAD.[7]

In this study, patients with PAD at the time of dialysis initiation had a worse prognosis than patients without PAD. Patients with PAD suffered more frequently from CVD and infectious diseases. After propensity score matching, all-cause mortality still indicated a similar result. As our propensity score included a history of coronary artery disease, we could not show a significant difference between patients with and without PAD regarding this aspect. We assume that the number of patients with PAD was too small to demonstrate a significant difference in infection-related deaths between patients with and without PAD. However, these results support that atherosclerosis is likely to occur not only in the coronary but also in the peripheral arteries in patients with ESKD. PAD is a systemic disease, which can negatively affect patients' prognosis. Based on our findings, it is critical to detect patients with PAD at the time of dialysis initiation.

Our results should be interpreted within the limitations of our study. Firstly, as this was an observational study, there is an inevitable selection bias in our patients with ESKD and PAD. Secondly, the number of patients with PAD was small, and not all patients

underwent peripheral angiography initially. Hence, the statistical power of our results may be low. Furthermore, we did not include patients with Fontaine stage I into the PAD group. However, our study included a well-defined population as a strength.

CONCLUSION

Patients with PAD at the time of dialysis initiation showed higher rates of mortality than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Acknowledgments

We acknowledge the support of the following members of the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) for this study: Hirofumi Tamai (Anjo Kosei Hospital), Tomohiko Naruse (Kasugai Municipal Hospital), Kei Kurata (Tosei General Hospital), Hideto Oishi (Komaki City Hospital), Isao Aoyama (Japan Community Healthcare Organization Chukyo Hospital), Hiroshi Ogawa (Shinseikai Daiichi Hospital), Hiroko Kushimoto (Nishichita General Hospital), Hideaki Shimizu (Chubu-Rosai Hospital), Junichiro Yamamoto (Tsushima City Hospital), Hisashi Kurata (Toyota Kosei Hospital), Taishi Yamakawa (Toyohashi Municipal Hospital), Takaaki Yaomura (Nagoya Medical Center), Hirotake Kasuga (Nagoya Kyouritsu Hospital), Shizunori Ichida (Japanese Red Cross Nagoya Daiichi Hospital), Hibiki Shinjo (Japanese Red Cross Nagoya Daini Hospital), Shigehisa Koide (Fujita Health University Hospital), and Yukio Yuzawa (Fujita Health University Hospital).

Individual author contributions

DI conceived and designed the study. DI developed the bespoke dataset. AT accessed the dataset, contributed to data analysis and interpretation, and provided feedback on the article. HM performed the data analysis and interpretation, wrote the first draft of the article, and subsequent revisions. SM contributed to study design, provided feedback on the article, and approved the submitted version. All authors have approved the final version for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

None declared.

Data availability statement

No additional data are available.

Patient and public involvement

No patients were involved.

REFERENCES

1. Sato T, Sakurai H, Okubo K, et al. Current state of dialysis treatment and vascular access management in Japan. *J Vasc Access* 2019;20:10–14. doi: 10.1177/1129729819838183.

2. Masakane I, Nakai S, Ogata S, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). *Ther Apher Dial* 2015;19:540–74. doi: 10.1111/1744-9987.12378.

3. Cozzolino M, Galassi A, Pivari F, et al. The cardiovascular burden in end-stage renal disease. *Contrib Nephrol* 2017;191:44–57. doi: 10.1159/000479250.

4. Cozzolino M, Mangano M, Stucchi A, et al. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018;33:iii28–iii34. doi: 10.1093/ndt/gfy174.

5. U.S. Renal Data System. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2009.

6. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003;64:603–9. doi: 10.1046/j.1523-1755.2003.00101.x.

7. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: Clinical synergy to improve outcomes. *Adv Chronic Kidney Dis* 2014;21:460–71. doi: 10.1053/j.ackd.2014.07.005.

8. Kumada Y, Aoyama T, Ishii H, et al. Long-term outcome of percutaneous transluminal angioplasty in chronic haemodialysis patients with peripheral artery disease. *Nephrol Dial Transplant* 2007;23:3996–4001. doi: 10.1093/ndt/gfn378.

9. Graziani L, Silvestro A, Bertone V, et al. Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. *Nephrol Dial Transplant* 2007;22:1144–9. doi: 10.1093/ndt/gfl764.

10. Otsubo S, Kitamura M, Wakaume T, et al. Association of peripheral artery disease and long-term mortality in hemodialysis patients. *Int Urol Nephrol* 2012:44:569–73. doi: 10.1007/s11255-010-9883-8.

11. Liew YP, Bartholomew JR, Demirjian S, et al. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. *Clin J Am Soc Nephrol* 2008;3:1084–9. doi: 10.2215/CJN.04411007.

12. O'Hare AM, Feinglass J, Sidawy AN, et al. Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 2003; 14:1287–95. doi: 10.1097/01.asn.0000061776.60146.02.

13. Liu JH, Chen JY, Lin SY, et al. Comparing survival between peritoneal dialysis and hemodialysis with subclinical peripheral artery disease: a 6-year follow up. *Int J Med Sci* 2013:10:434–40. doi: 10.7150/ijms.5091.

14. Hishida M, Tamai H, Morinaga T, et al. Aichi cohort study of the prognosis in patients newly initiated into dialysis (AICOPP): baseline characteristics and trends observed in diabetic nephropathy. *Clin Exp Nephrol* 2016;20:795–807. doi: 10.1007/s10157-015-1206-z.

15. Lee CC, Wu CJ, Chou LH, et al. Peripheral artery disease in peritoneal dialysis and hemodialysis patients: single-center retrospective study in Taiwan. *BMC Nephrol* 2012:13:100. doi: 10.1186/1471-2369-13-100.

16. Tanaka A, Inaguma D, Shinjo H, et al. Presence of atrial fibrillation at the time of dialysis initiation is associated with mortality and cardiovascular events. *Nephron* 2016;132:86–92. doi: 10.1159/000443314.

17. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders [in German]. *Helv Chir Acta* 1954;21:499–533.

18. Ho DE, Imai K, King G, et al. MatchIt: Nonparametric preprocessing for parametric causal inference. *J Stat Soft* 2011:42:1–28.

19. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92. doi: 10.1053/j.ajkd.2008.12.034.

20. Cooper BA, Penne EL, Bartlett LH, et al. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kidney Dis* 2004:43:61–6. doi: 10.1053/j.ajkd.2003.08.045.

Figure legends

Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

Figure 2. Kaplan-Meier plot for all-cause death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

Figure 3. Kaplan-Meier plot for CVD-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease; CVD, cardiovascular disease.

Figure 4. Kaplan-Meier plot for infection-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

Figure 5. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

Figure 6. Kaplan-Meier plot for all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

Figure 7. Kaplan-Meier plot for CVD-related death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. CVD, cardiovascular disease; PAD, peripheral artery disease; PSM, propensity score matching.

Figure 8. Kaplan-Meier plot for infection-related death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

Figure 9. Hazard ratio of PAD for all-cause death in propensity score-matched patients (n = 284) who started dialysis. HR, hazard ratio.; PAD, peripheral artery disease; Pre SBP, systolic blood pressure before dialysis.

Figure 1.

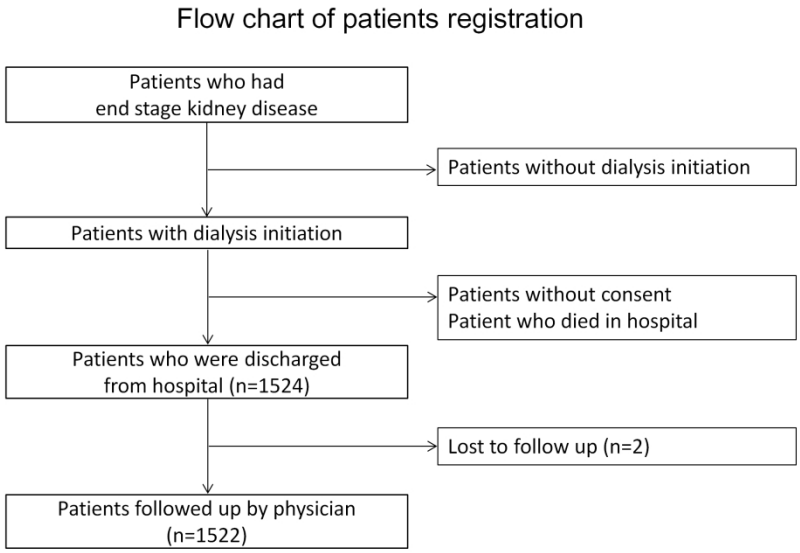


Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

254x190mm (300 x 300 DPI)

Figure 2.

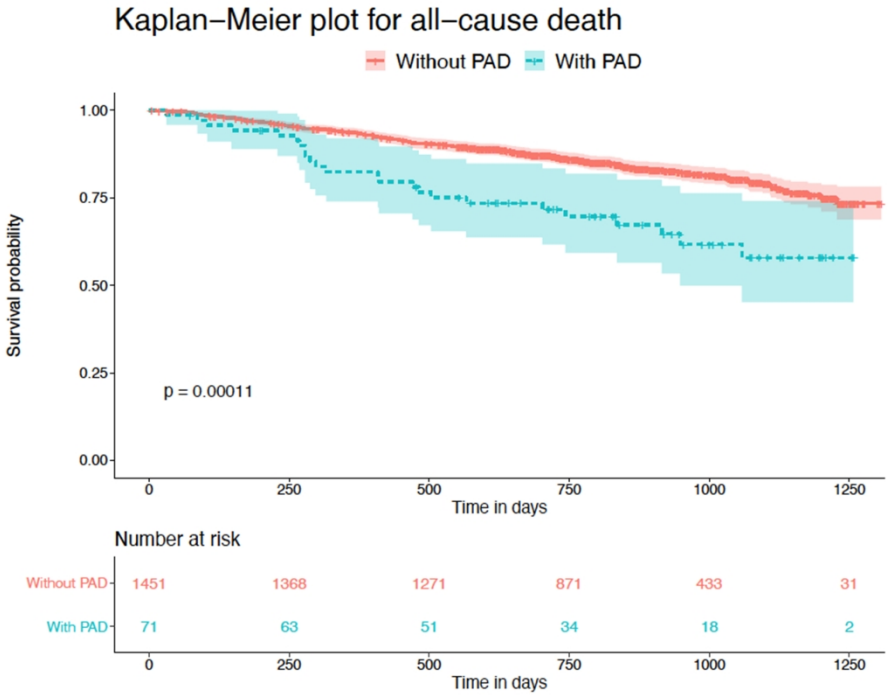


Figure 2. Kaplan-Meier plot for all-cause death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

254x190mm (300 x 300 DPI)

Figure 3.

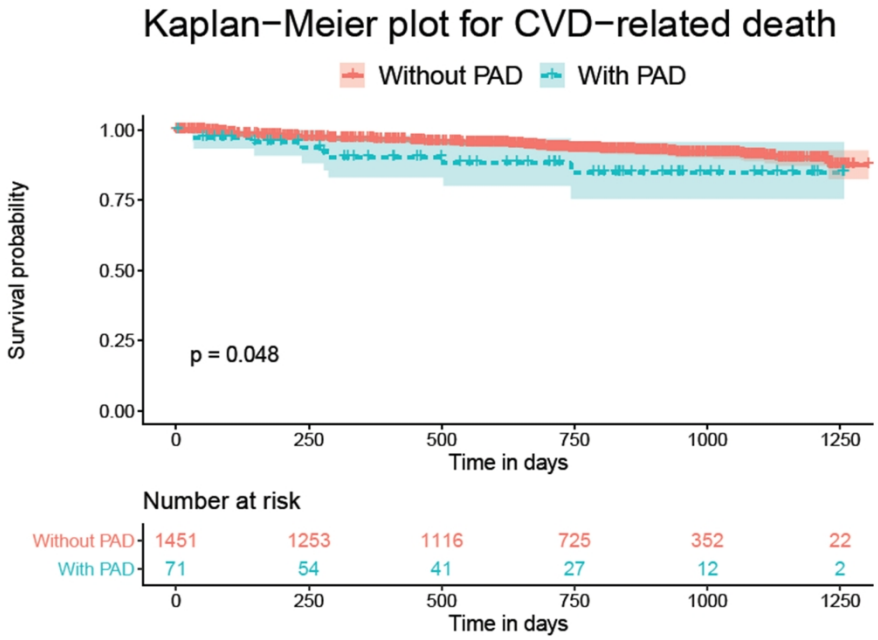


Figure 3. Kaplan-Meier plot for CVD-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease; CVD, cardiovascular disease.

254x190mm (300 x 300 DPI)

Figure 4.

Figure 4. Kaplan-Meier plot for infection-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

254x190mm (300 x 300 DPI)

Figure 5.

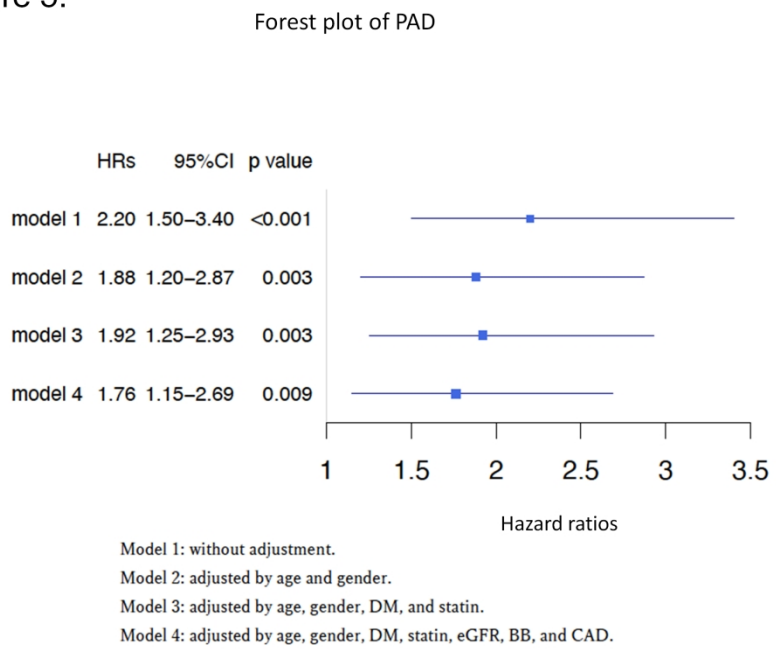


Figure 5. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

254x190mm (300 x 300 DPI)

Figure 6.

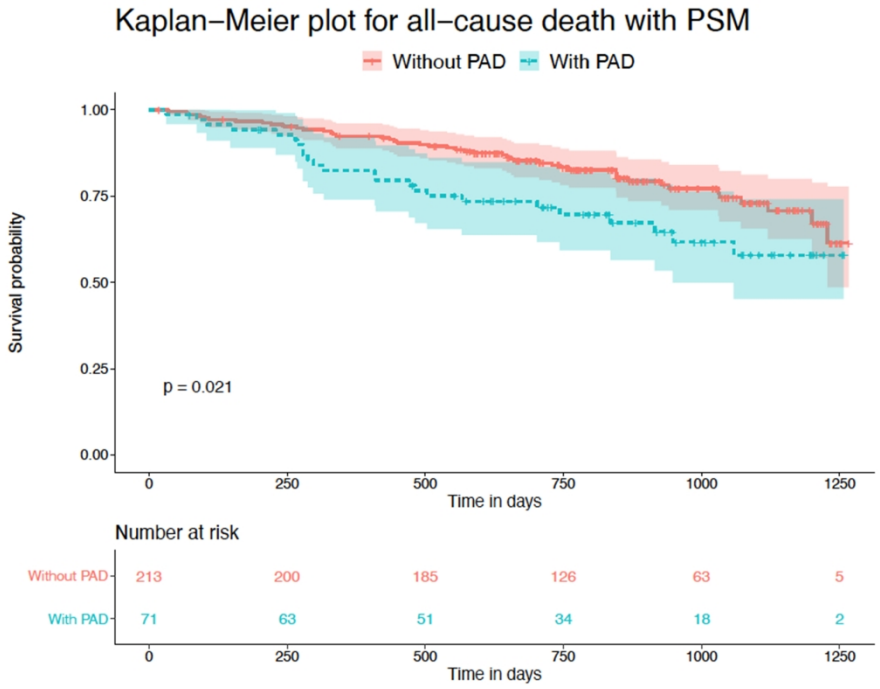


Figure 6. Kaplan-Meier plot for all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

254x190mm (300 x 300 DPI)

Figure 7.

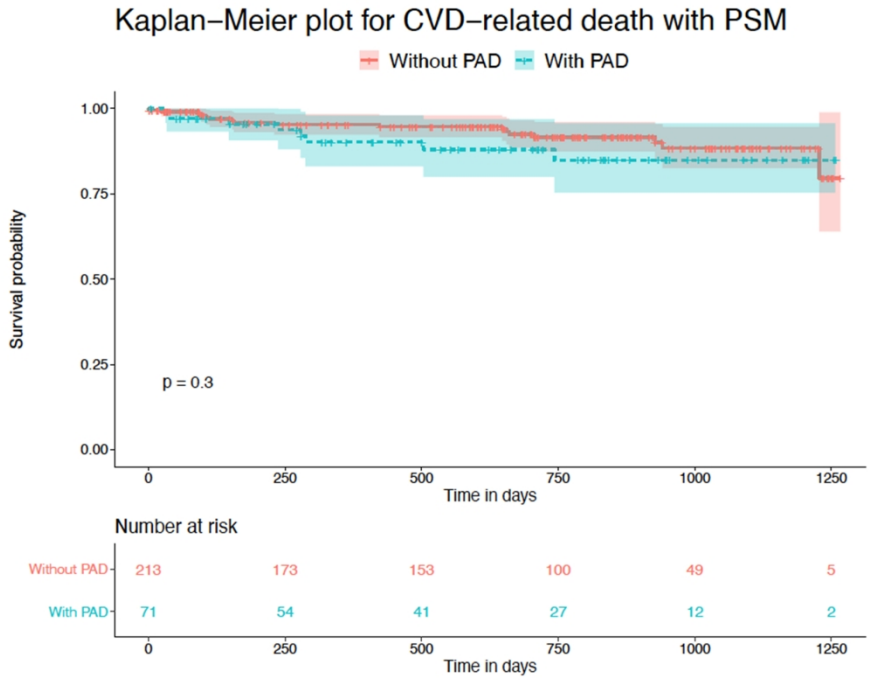


Figure 7. Kaplan-Meier plot for CVD-related death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. CVD, cardiovascular disease; PAD, peripheral artery disease; PSM, propensity score matching.

254x190mm (300 x 300 DPI)

Figure 8.

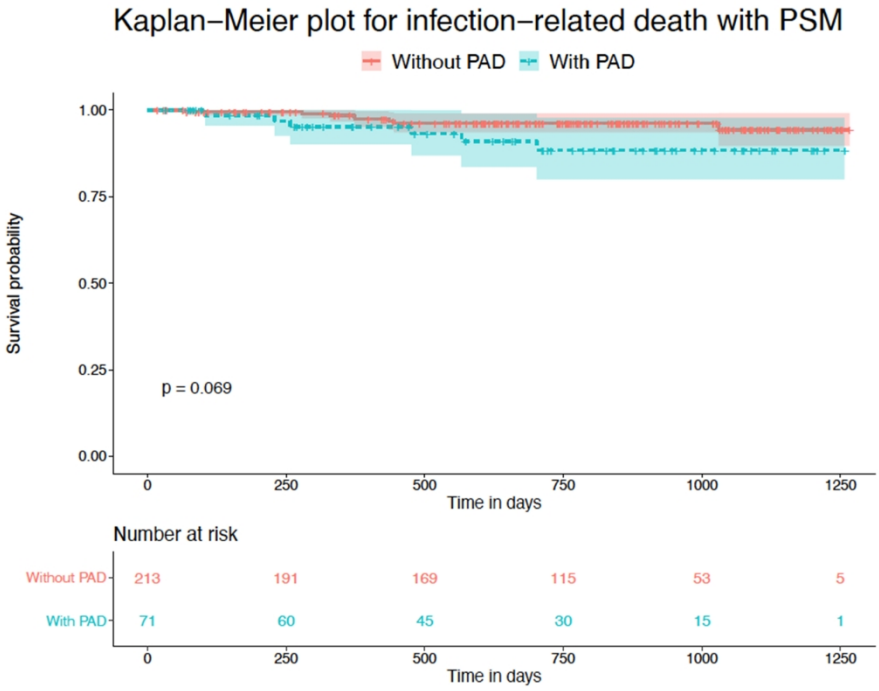


Figure 8. Kaplan-Meier plot for infection-related death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

254x190mm (300 x 300 DPI)

Figure 9.

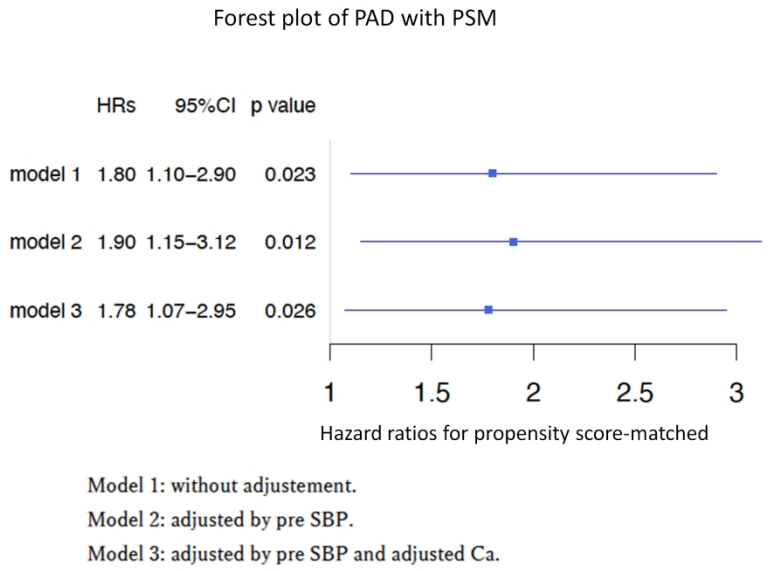


Figure 9. Hazard ratio of PAD for all-cause death in propensity score-matched patients (n = 284) who started dialysis. HR, hazard ratio.; PAD, peripheral artery disease; Pre SBP, systolic blood pressure before dialysis.

254x190mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7, Figure 1
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Figure 1
		(b) Give reasons for non-participation at each stage	7, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 5
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042315.R1
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2020
Complete List of Authors:	Morooka, Hikaru; Nagoya University Hospital, Nephrology Tanaka, Akihito; Nagoya University Hospital, Nephrology Inaguma , D.; Fujita Health University, Nephrology Maruyama, Shoichi; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Hikaru Morooka,[1] Akihito Tanaka,[1] Daijo Inaguma[2], Shoichi Maruyama[3]

[1]Division of Nephrology, Nagoya University Hospital, Nagoya, Japan

[2] Division of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan

[3]Division of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Corresponding author: Akihito Tanaka

Division of Nephrology,

Nagoya University Hospital

Tsurumaicho, 65, Showa Ward, Nagoya, Aichi, Japan

Tel: +81-52-741-2111

Fax: +81-52-744-2209

E-mail: tanaka17@med.nagoya-u.ac.jp

Word count: 3120.

ABSTRACT

Objectives: Patients with peripheral artery disease (PAD) are reported to have a poorer prognosis than those without PAD. PAD is sometimes found at dialysis initiation, but its influence on the prognosis in these patients has not been investigated. We aimed to compare the mortality between patients with PAD at the time of dialysis initiation and those without PAD.

Design: We undertook an observational prospective multicenter study of patients starting dialysis therapy. Data were collected on patients' sex, age, presence of PAD, medication, past medical history, and clinical and laboratory data.

Setting: Seventeen centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis.

Participants: A total of 1524 patients with chronic kidney disease who started dialysis from October 2011 to September 2013. The patients were followed up until March 2015. During this time, there were two patients lost to follow-up.

Primary and secondary outcome measures: The primary outcome was defined as all-cause death. The secondary outcomes were defined as each cause of death**.**

Results: The study included 1030 men and 492 women with a mean age of 67.5 ± 13.1 years. Of these, 71 had PAD, and 1451 did not. After a median follow-up of 814.5 days, 33.8 % of the former and 17.0 % of the latter group had died by March 2015 ($p < 0.01$). After adjusting for confounding factors, PAD at dialysis initiation remained an independent risk factor for mortality ($p < 0.01$).

Conclusions: Patients with PAD at the time of dialysis initiation had a poorer prognosis than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Key words: Chronic kidney diseases; Dialysis; Mortality; Peripheral artery disease

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This observational prospective multicenter study analyzed data in patients at the beginning of dialysis and for a median follow-up of 814.5 days.
- Our study had a high follow-up rate (only two patients lost to follow-up) and a well-defined population with comprehensive data at the start of dialysis.
- The number of patients with PAD at the initiation of dialysis was comparably small, and not all of them underwent other tests such as, contrast-enhanced computed tomography, magnetic resonance angiography, and peripheral angiography to confirm the diagnosis.

INTRODUCTION

The number of patients receiving dialysis therapy is increasing every year, and these patients have a high mortality risk from various causes, particularly cardiovascular diseases (CVD).[1, 2] End-stage kidney disease (ESKD) represents a considerable risk of atherosclerosis, and patients on dialysis tend to have further risk factors contributing to the rapid deterioration of CVD.[3] While CVD, including stroke, and coronary artery disease have been reported in more detail in patients on dialysis,[4-6] the problem of peripheral artery disease (PAD) in patients undergoing dialysis therapy has been less frequently addressed. With both aging and a growing number of diabetic patients on dialysis, the prevalence of PAD among these patients is likely to increase year by year.[7] PAD with distal lesions is more common in patients with ESKD, making the transarterial approach to the stenosis sometimes difficult.[8, 9] Furthermore, a vascular stenosis can promote peripheral ischemic skin ulcers or gangrene, leading to an intractable pathology. Thus, patients with PAD on dialysis therapy have a worse prognosis than those without PAD.[10] Consequently, there is an urgent need to clarify the relationships between PAD and mortality in patients on dialysis. Furthermore, to improve the prognosis of dialysis patients, it is crucial to understand the characteristics of those with high mortality risk.

The classic atherosclerosis risk factors, such as age, smoking, diabetes, hypertension, and hyperlipidemia, are common in patients with ESKD, but their chronic kidney disease (CKD) condition adds unique risk factors that promote PAD: chronic inflammation, hypoalbuminemia, and a pro-calcific state. PAD in ESKD patients markedly increases the possibility of myocardial ischemia and stroke, and is the main cause of limb loss and mortality, the rates of which are much higher than those in the general population.[10,11] Moreover, it has been pointed out that if patients with PAD develop critical limb ischemia, their overall survival is worse than that of patients with malignant tumors.[12] Hence, when considering the prognosis of patients receiving dialysis, the presence of PAD is important.

There are few recent reports on PAD in patients with ESKD at the time of dialysis initiation. Several studies have investigated patients receiving maintenance dialysis. In these studies, descriptive data included the prognosis of "only maintenance dialysis" patients.[10, 13-15] According to them, PAD had an overall prevalence of 18.2 %, and the patient survival rate was 28.6 % during 8.8 years in the PAD group. Moreover, since these studies focused on patients on maintenance dialysis, they mainly addressed PAD that occurred during dialysis. However, renal function in patients with CKD may decrease during the treatment of PAD. At other times, PAD is found when investigating the cause of renal function deterioration or when screening patients for their eligibility for a renal transplant. PAD at the time of dialysis initiation is a complex and clinically relevant problem.

In the present study, we compared PAD and non-PAD patients who had started dialysis therapy in the Aichi prefecture to identify the mortality associated with PAD in ESKD patients at the time of initiation of dialysis therapy.

PATIENTS AND METHODS

Patient registration and data collection

Data from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis [14, 16] were used in this prospective multicenter study. Patients who started dialysis between October 2011 and September 2013 at 17 Japanese institutions were eligible for participation. This study was approved by the Ethics Committee of the Institutional Review Board in Nagoya University (Approval number 1335), and all patients provided written informed consent.

First, we screened all patients with ESKD in whom dialysis was initiated. Only patients who became stable and were discharged or transferred from the hospital were included. Patients who were not discharged and died in the hospital were excluded (Figure 1). Data regarding patients' demographics, medical history, comorbidities, medications, and laboratory data

during the period of dialysis initiation were collected. PAD was clinically diagnosed based on symptoms, physical findings, and various examinations, but not all patients received angiography for diagnosis. After physicians carefully evaluated patients, we used the Fontaine classification for grading of severity. [17] The presence of PAD was defined as a Fontaine stage II or higher. Laboratory data were obtained immediately prior to the first dialysis session. Patients were followed by survey slips sent to the dialysis facilities until the end of March 2015.

Patient and public involvement

Patients were not involved at any stage of the research for this study.

Mortality

Patients were divided into one group with PAD and one group without PAD. The primary endpoint was all-cause mortality. Causes of death were recorded to the extent possible. The occurrence of death was investigated via survey slips sent to the dialysis facilities at the end of March 2015.

We compared the outcomes, hazard ratios (HRs) and logistic regression model between the two groups.

Statistics

Baseline characteristics were presented descriptively and compared between the two groups using the Student's *t*-test or χ^2-test. Survival was presented graphically using the Kaplan-Meier method and analyzed using uni- and multivariate Cox regression, and uni- and multivariate logistic regression model. HRs were calculated and presented graphically using forest plots. Odds ratios (ORs) were calculated and presented on a table. We used propensity score

matching to account for differences in baseline characteristics between the two groups. The propensity score was calculated based on age, sex, presence of diabetes, medication (use of statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, and antiplatelets), laboratory data (levels of phosphorus, hemoglobin, and estimated glomerular filtration rate), and history of coronary artery disease.

P-values of < 0.05 were considered to be statistically significant. We used the R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/) for all statistical analysis. For the propensity score matching, the R-package MatchIt (1:3 matching with the nearest neighbor) was used.[18] Missing data were not complemented, however the characteristics we used for propensity score matching were not missing.

RESULTS

Baseline characteristics

Patients' baseline characteristics are shown in Table 1. The initial population included 1524 participants, of whom 1032 were men, and 492 were women. The mean age was 67.5 ± 13.1 years. Two patients were untraceable and lost to follow-up. Of the remaining 1522 patients, 71 (4.7%) had PAD, and 1451 did not. There were significant differences between patients with and without PAD with regard to comorbidities and drug use. Antiplatelet administration was significantly more frequent in those with PAD than in those without PAD. This may be because treatment for PAD includes antiplatelets. However, since other causes, such as myocardial infarction, can be the reason why these patients were on the antiplaltelet therapy. The prevalence of diabetes mellitus, coronary artery disease, and aortic dissection was significantly higher in those with than in those without PAD. Patients with PAD had significantly lower ejection fractions than patients without PAD. The use of both beta-blockers and statins was

significantly higher in patients with PAD than in those without PAD (beta-blockers: 34.0 % and 47.9 %, respectively, p = 0.024; statins: 39.4 % and 53.5 %, respectively, p = 0.024). The estimated glomerular filtration rate [19] was significantly higher in patients with PAD than in those without PAD (6.34 ± 1.83 mL/min per 1.7 m^2 and 5.40 ± 2.23 mL/min per 1.7m^2, respectively, p < 0.001).

The median follow-up was 814.5 days (interquartile range 645-1037).

Mortality

During the follow-up period, 271 patients died from various causes, including cardiovascular events (102 patients, 37.6 %), infectious disease (56 patients, 20.7 %), cancer (45 patients, 16.6 %), and other causes. The PAD group had a significantly higher mortality rate of 33.8 % than the group without PAD with 17.0 % (p < 0.01; Table 1). Figure 2 shows the Kaplan-Meier plot for all-cause mortality in patients with and without PAD.

Table 1. Baseline and clinical characteristics and outcomes of patients starting dialysis (n = 1522)

	Patients without PAD(n = 1451)	Patients with PAD (n= 71)	P value
Female (%)	33.1	16.9	0.007
Age (years) (mean (SD))	67.4 (13.1)	69.9 (12.1)	0.106
Past history			
Diabetes (%)	50.2	67.6	0.006
CAD (%)	15.9	36.6	<0.001
PCI (%)	9.6	21.1	0.003

CABG (%)	3.8	14.1	<0.001
Aortic dissection (%)	5.0	15.5	<0.001
Admission of HF (%)	19.4	42.3	<0.001
Stroke (%)	9.1	7.0	0.704
Cause of CKD			0.294
Diabetes (%)	42.5	59.2	
Nephrosclerosis (%)	25.3	25.4	
CGN (%)	15.6	4.2	
Others, unknown (%)	4.3	4.2	
Vital data			
Pre-dialysis SBP (mmHg) (mean (SD))	151.1 (25.9)	151.7 (29.5)	0.843
Cardiac ultrasonography			
EF (%) (mean (SD))	60.9 (12.2)	55.8 (13.7)	0.001
Chest X-ray			
CTR (%) (mean (SD))	55.2 (7.2)	55.2 (7.1)	0.973
Administration			
ARB or ACEI (%)	60.6	56.3	0.554
BB (%)	34.0	47.9	0.024
Statin (%)	39.4	53.5	0.024
VDRA (%)	26.9	29.6	0.726
Antiplatelets (%)	28.9	56.3	<0.001
ESA (%)	85.8	87.3	0.861

Laboratory data

WBC (/uL) (mean (SD))	6729.88 (3130.80)	7206.62 (3581.54)	0.214
Hb (g/dL) (mean (SD))	9.37 (1.55)	9.40 (1.45)	0.887
Plt (10 000/uL) (mean (SD))	18.24 (7.62)	18.17 (8.19)	0.943
Alb (g/dL) (mean (SD))	3.21 (0.59)	3.02 (0.62)	0.010
BUN (mg/dL) (mean (SD))	92.02 (30.69)	86.68 (24.84)	0.149
Cr (mg/dL) (mean (SD))	9.03 (3.24)	7.74 (2.22)	0.001
eGFR (mL/min/1.73m^2) (mean (SD))	5.40 (2.23)	6.34 (1.83)	0.001
Na (mEq/L) (mean (SD))	137.88 (4.41)	137.93 (3.91)	0.933
K (mEq/L) (mean (SD))	4.56 (0.84)	4.43 (0.81)	0.194
Adjusted Ca (mg/dL) (mean (SD))	8.59 (1.06)	9.06 (0.93)	<0.001
P (mg/dL) (mean (SD))	6.40 (1.89)	5.76 (1.56)	0.005
Mg (mg/dL) (mean (SD))	2.15 (0.49)	2.17 (0.44)	0.826
UA (mg/dL) (mean (SD))	8.80 (2.44)	8.64 (2.27)	0.582
LDL C (mg/dL) (mean (SD))	89.97 (34.25)	87.08 (37.14)	0.525
CRP (mg/dL) (mean (SD))	1.82 (4.14)	2.39 (4.68)	0.271
β2MG (ng/dL) (mean (SD))	19.32 (5.78)	17.33 (5.05)	0.027
TSAT (%) (mean (SD))	27.16 (16.60)	25.44 (17.95)	0.438
Ferritin (ng/dL) (mean (SD))	222.28 (1009.80)	226.65 (395.74)	0.972

Outcome			
Infection-related death (%)	3.4	8.5	0.062
CVD-related death (%)	6.6	11.6	0.167
All-cause death (%)	17.0	33.8	0.001

ACEI; angiotensin-converting enzyme inhibitor. Adjusted Ca; adjusted calcium. Alb; albumin. ARB; angiotensin receptor blocker. BB; beta blocker. BUN; blood urea nitrogen. β 2MG; beta-2 microglobulin. Ca; calcium. CABG; coronary artery bypass grafting. CAD; coronary artery disease. CGN; chronic glomerulonephritis. CKD; chronic kidney disease. Cr; creatinine. CRP; C-reactive protein. CTR; cardiothoracic ratio. CVD; cardiovascular disease. EF; ejection fraction. eGFR; estimated glomerular filtration rate. ESA; erythropoietin stimulating agent. Hb; hemoglobin. HF; heart failure. K; potassium. LDL-C; low-density lipoprotein cholesterol. Mg; magnesium. Na; sodium. P; phosphate. PAD; peripheral arterial disease. PCI; percutaneous coronary intervention. Plt; platelet. SBP; systolic blood pressure. SD; standard deviation. TSAT; transferrin saturation. UA; uric acid. VDRA; Vitamin D receptor agonist. WBC; white blood cells.

Figure 3 shows the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p = 0.048). Figure 4 shows the Kaplan-Meier plot for infection-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p = 0.011). Figure 5 shows the forest plot for the HRs of PAD for all-cause death with adjustment for confounding factors. PAD was an independent risk factor for death (HR, 1.76;

95 % confidence interval, 1.15–2.69; $p < 0.01$). As sensitivity analyses, we conducted the same analyses on patients, who survived longer than 3 months after the observation beginning. The results resembled the former ones (Supplemental figure 1, 3, 4), except the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD ($p = 0.094$; Supplemental figure 2).

Propensity score-matched comparison between patients with and without PAD

The baseline and clinical characteristics in Table 1 showed significant differences between patients in the group with and without PAD, suggesting that there was a possibility of bias. Table 2 shows the baseline characteristics of the propensity score-matched patients with (n=71) and without PAD (n=213).

Table 2. Baseline and clinical characteristics and outcomes of propensity-score matched patients starting dialysis (n = 284)

	Patients without PAD (n = 213)	Patients with PAD (n = 71)	P value
Female (%)	15.0	16.9	0.850
Age (years) (mean (SD))	69.1 (12.2)	69.9 (12.1)	0.607
Past history			
DM (%)	67.1	67.6	1.000
CAD (%)	40.4	36.6	0.674
PCI (%)	26.8	21.1	0.431
CABG (%)	9.9	14.1	0.442
Aortic dissection (%)	7.0	15.5	0.057
Admission of HF (%)	29.1	42.3	0.057

Stroke (%)	14.1	7.0	0.175
Cause of CKD			0.091
Diabetes (%)	58.7	59.2	
Nephrosclerosis (%)	25.4	25.4	
CGN (%)	8.5	4.2	
Others, unknown (%)	2.3	4.2	
Vital data			
Pre-dialysis SBP (mmHg) (mean (SD))	151.8 (28.3)	151.7 (29.5)	0.977
Cardiac ultrasonography			
EF (%) (mean (SD))	59.8 (13.8)	55.8 (13.7)	0.049
Chest X-ray			
CTR (%) (mean (SD))	55.3 (6.8)	55.2 (7.1)	0.885
Administration			
ARB or ACEI (%)	59.2	56.3	0.781
BB (%)	49.3	47.9	0.945
Statin (%)	58.7	53.5	0.533
VDRA (%)	27.2	29.6	0.819
Antiplatelets (%)	58.2	56.3	0.89
ESA (%)	89.7	87.3	0.742
Laboratory data			
WBC (/uL) (mean (SD))	6704.76 (2722.41)	7206.62 (3581.54)	0.217
Hb (g/dL) (mean (SD))	9.62 (1.43)	9.40 (1.45)	0.275
Plt (10 000/uL) (mean (SD))	17.90 (7.39)	18.17 (8.19)	0.796
Alb (g/dL) (mean (SD))	3.20 (0.60)	3.02 (0.62)	0.032

BUN (mg/dL) (mean (SD))	87.14 (27.58)	86.68 (24.84)	0.901
Cr (mg/dL) (mean (SD))	8.47 (2.82)	7.74 (2.22)	0.049
eGFR (mL/min/1.73m^2) (mean (SD))	6.05 (2.47)	6.34 (1.83)	0.368
Na (mEq/L) (mean (SD))	138.36 (4.56)	137.93 (3.91)	0.475
K (mEq/L) (mean (SD))	4.51 (0.83)	4.43 (0.81)	0.492
Adjusted Ca (mg/dL) (mean (SD))	8.71 (0.96)	9.06 (0.93)	0.007
P (mg/dL) (mean (SD))	5.96 (1.63)	5.76 (1.56)	0.372
Mg (mg/dL) (mean (SD))	2.22 (0.46)	2.17 (0.44)	0.497
UA (mg/dL) (mean (SD))	8.75 (2.49)	8.64 (2.27)	0.731
LDL C (mg/dL)(mean (SD))	87.07 (32.01)	87.08 (37.14)	0.999
CRP (mg/dL) (mean (SD))	1.61 (3.30)	2.39 (4.68)	0.137
β2MG (ug/dL) (mean (SD))	17.95 (5.04)	17.33 (5.05)	0.497
TSAT (%) (mean (SD))	25.41 (14.74)	25.44 (17.95)	0.992
Ferritin (ng/dL) (mean (SD))	171.44 (208.99)	226.65 (395.74)	0.153
Outcome			
Infection-related death (%)	3.8	8.5	0.206
CVD-related death (%)	8.2	11.6	0.537
All-cause death (%)	21.6	33.8	0.056

ACEI; angiotensin-converting enzyme inhibitor. Adjusted Ca; adjusted calcium. Alb; albumin. ARB; angiotensin receptor blocker. BB; beta blocker. BUN; blood urea nitrogen. β 2MG; beta-2 microglobulin. Ca; calcium. CABG; coronary artery bypass grafting. CAD; coronary artery

disease. CGN; chronic glomerulonephritis. CKD; chronic kidney disease. Cr; creatinine. CRP; C-reactive protein. CTR; cardiothoracic ratio. CVD; cardiovascular disease. EF; ejection fraction. eGFR; estimated glomerular filtration rate. ESA; erythropoietin stimulating agent. Hb; hemoglobin. HF; heart failure. K; potassium. LDL-C; low-density lipoprotein cholesterol. Mg; magnesium. Na; sodium. P; phosphate. PAD; peripheral arterial disease. PCI; percutaneous coronary intervention. Plt; platelet. SBP; systolic blood pressure. SD; standard deviation. TSAT; transferrin saturation. UA; uric acid. VDRA; Vitamin D receptor agonist. WBC; white blood cells.

Figure 6 shows the Kaplan-Meier plot for all-cause death in matched patients with and without PAD. Patients with PAD showed a significantly worse prognosis than those without. For CVD-related and infection-related death, respectively, in matched patients with and without PAD with no significant differences between the groups ($p = 0.3$, $p = 0.069$). In logistic regression analysis including propensity score into multivariable factors, patients with PAD had significantly worse prognosis than patients without PAD (Table 3).

Table 3. Odds ratios of the mortality of the patients (n = 1522)

	Odds Ratio	95% CI	p value
Model 1	2.4891033	1.4940416 - 4.1468959	0.000462
Model 2	1.9968599	1.1813227 - 3.3754108	0.00982
Model 3	2.1169338	1.2413296 - 3.6101681	0.005891
Model 4	1.927411	1.12468268 - 3.3030767	0.016962

Model 1: PAD

Model 2: PAD + propensity score

Model 3: PAD + propensity score + pre SBP

Model 4: PAD + propensity score + pre SBP + adjusted Calcium

CI; confidence interval. PAD; peripheral artery disease. SBP; systolic blood pressure

DISCUSSION

Our study showed that patients with PAD at the time of dialysis initiation had a significantly higher mortality than patients without PAD. This higher risk should be considered in the treatment and monitoring of these patients.

A previous study suggested that the prevalence of PAD in patients with ESKD reached almost 20 %.[15] In our cohort, the prevalence of PAD was much lower, most likely because our patients started dialysis, whereas the patients in the literature where on maintenance dialysis. This might reflect a deterioration of peripheral atherosclerosis with longer duration of dialysis. Another study suggested that the chronic uremic state is associated with systemic inflammation in dialysis patients, leading to hypoalbuminemia and an increased risk of PAD.[20] Hence, our results are remarkable because we showed the prevalence of PAD at the time of dialysis initiation, while past studies reported on PAD during maintenance dialysis. Furthermore, patients with PAD in our study more frequently had a decreased ejection fraction and decreased albumin and increased adjusted calcium levels than those without PAD, even after propensity score matching. We cannot exclude the possibility of other factors associated with PAD that were not corrected even after our propensity score matching. This implies that PAD is one symptom of a systemic atherosclerotic disease that affects not only the peripheral

but also coronary arteries. When seeing patients with myocardial infarction or low cardiac systolic function, it is recommended to suspect that they have PAD.[7]

In this study, patients with PAD at the time of dialysis initiation had a worse prognosis than patients without PAD. Patients with PAD suffered more frequently from CVD and infectious diseases. After propensity score matching, all-cause mortality still indicated a similar result. As our propensity score included a history of coronary artery disease, we could not show a significant difference between patients with and without PAD regarding this aspect. We assume that the number of patients with PAD was too small to demonstrate a significant difference in infection-related deaths between patients with and without PAD. However, these results support that atherosclerosis is likely to occur not only in the coronary but also in the peripheral arteries in patients with ESKD. PAD is a systemic disease, which can negatively affect patients' prognosis. Based on our findings, it is critical to detect patients with PAD at the time of dialysis initiation.

Our results should be interpreted within the limitations of our study. Firstly, as this was an observational study, there is an inevitable selection bias in our patients with ESKD and PAD. Secondly, the number of patients with PAD was small, the number of patients who received the ankle brachial index is not available. Not all patients underwent other diagnostic tests such as contrast-enhanced computed tomography, magnetic resonance angiography, and peripheral angiography initially. Hence, the statistical power of our results may be low. Furthermore, we did not include patients with Fontaine stage I into the PAD group. However, our study included a well-defined population as a strength.

CONCLUSION

Patients with PAD at the time of dialysis initiation showed higher rates of mortality than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Acknowledgments

We acknowledge the support of the following members of the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) for this study: Hirofumi Tamai (Anjo Kosei Hospital), Tomohiko Naruse (Kasugai Municipal Hospital), Kei Kurata (Tosei General Hospital), Hideto Oishi (Komaki City Hospital), Isao Aoyama (Japan Community Healthcare Organization Chukyo Hospital), Hiroshi Ogawa (Shinseikai Daiichi Hospital), Hiroko Kushimoto (Nishichita General Hospital), Hideaki Shimizu (Chubu-Rosai Hospital), Junichiro Yamamoto (Tsushima City Hospital), Hisashi Kurata (Toyota Kosei Hospital), Taishi Yamakawa (Toyohashi Municipal Hospital), Takaaki Yaomura (Nagoya Medical Center), Hirotake Kasuga (Nagoya Kyouritsu Hospital), Shizunori Ichida (Japanese Red Cross Nagoya Daiichi Hospital), Hibiki Shinjo (Japanese Red Cross Nagoya Daini Hospital), Shigehisa Koide (Fujita Health University Hospital), and Yukio Yuzawa (Fujita Health University Hospital).

Individual author contributions

DI conceived and designed the study. DI developed the bespoke dataset. AT accessed the dataset, contributed to data analysis and interpretation, and provided feedback on the article. HM performed the data analysis and interpretation, wrote the first draft of the article, and subsequent revisions. SM contributed to study design, provided feedback on the article, and approved the submitted version. All authors have approved the final version for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

None declared.

Data availability statement

No additional data are available.

Patient and public involvement

No patients were involved.

REFERENCES

1. Sato T, Sakurai H, Okubo K, et al. Current state of dialysis treatment and vascular access management in Japan. *J Vasc Access* 2019;20:10–14. doi: 10.1177/1129729819838183.

2. Masakane I, Nakai S, Ogata S, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). *Ther Apher Dial* 2015;19:540–74. doi: 10.1111/1744-9987.12378.

3. Cozzolino M, Galassi A, Pivari F, et al. The cardiovascular burden in end-stage renal disease. *Contrib Nephrol* 2017;191:44–57. doi: 10.1159/000479250.

4. Cozzolino M, Mangano M, Stucchi A, et al. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018;33:iii28–iii34. doi: 10.1093/ndt/gfy174.

5. U.S. Renal Data System. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2009.

6. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003;64:603–9. doi: 10.1046/j.1523-1755.2003.00101.x.

7. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: Clinical synergy to improve outcomes. *Adv Chronic Kidney Dis* 2014;21:460–71. doi: 10.1053/j.ackd.2014.07.005.

8. Kumada Y, Aoyama T, Ishii H, et al. Long-term outcome of percutaneous transluminal angioplasty in chronic haemodialysis patients with peripheral artery disease. *Nephrol Dial Transplant* 2007;23:3996–4001. doi: 10.1093/ndt/gfn378.

9. Graziani L, Silvestro A, Bertone V, et al. Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. *Nephrol Dial Transplant* 2007;22:1144–9. doi: 10.1093/ndt/gfl764.

10. Otsubo S, Kitamura M, Wakaume T, et al. Association of peripheral artery disease and long-term mortality in hemodialysis patients. *Int Urol Nephrol* 2012:44:569–73. doi: 10.1007/s11255-010-9883-8.

11. Liew YP, Bartholomew JR, Demirjian S, et al. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. *Clin J Am Soc Nephrol* 2008;3:1084–9. doi: 10.2215/CJN.04411007.

12. O'Hare AM, Feinglass J, Sidawy AN, et al. Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 2003; 14:1287–95. doi: 10.1097/01.asn.0000061776.60146.02.

13. Liu JH, Chen JY, Lin SY, et al. Comparing survival between peritoneal dialysis and hemodialysis with subclinical peripheral artery disease: a 6-year follow up. *Int J Med Sci* 2013:10:434–40. doi: 10.7150/ijms.5091.

14. Hishida M, Tamai H, Morinaga T, et al. Aichi cohort study of the prognosis in patients newly initiated into dialysis (AICOPP): baseline characteristics and trends observed in diabetic nephropathy. *Clin Exp Nephrol* 2016;20:795–807. doi: 10.1007/s10157-015-1206-z.

15. Lee CC, Wu CJ, Chou LH, et al. Peripheral artery disease in peritoneal dialysis and hemodialysis patients: single-center retrospective study in Taiwan. *BMC Nephrol* 2012:13:100. doi: 10.1186/1471-2369-13-100.

16. Tanaka A, Inaguma D, Shinjo H, et al. Presence of atrial fibrillation at the time of dialysis initiation is associated with mortality and cardiovascular events. *Nephron* 2016;132:86–92. doi: 10.1159/000443314.

17. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders [in German]. *Helv Chir Acta* 1954;21:499–533.

18. Ho DE, Imai K, King G, et al. MatchIt: Nonparametric preprocessing for parametric causal inference. *J Stat Soft* 2011:42:1–28.

19. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92. doi: 10.1053/j.ajkd.2008.12.034.

20. Cooper BA, Penne EL, Bartlett LH, et al. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kidney Dis* 2004:43:61–6. doi: 10.1053/j.ajkd.2003.08.045.

Figure legends

Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

Figure 2. Kaplan-Meier plot for all-cause death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

Figure 3. Kaplan-Meier plot for CVD-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease; CVD, cardiovascular disease.

Figure 4. Kaplan-Meier plot for infection-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

Figure 5. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

Figure 6. Kaplan-Meier plot for all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

Supplement figure legends

Supplemental figure 1:

The Kaplan-Meier plot for all-cause death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.

Supplemental figure 2:

The Kaplan-Meier plot for CVD-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease; CVD, cardiovascular disease.

Supplemental figure 3:

The Kaplan-Meier plot for infection-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.

Supplemental figure 4:

Hazard ratio of PAD for all-cause death in patients who survived longer than 3 months after the dialysis beginning (n = 1504). HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

Figure 1.

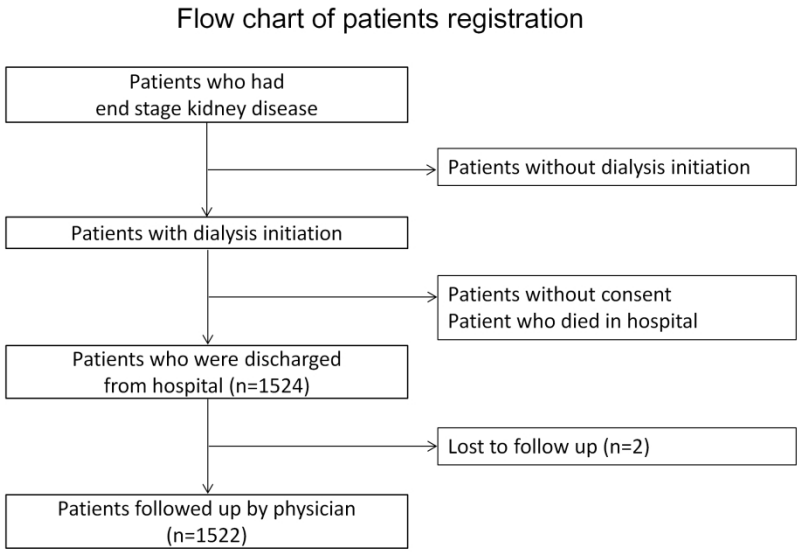


Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

254x190mm (300 x 300 DPI)

Figure 2.

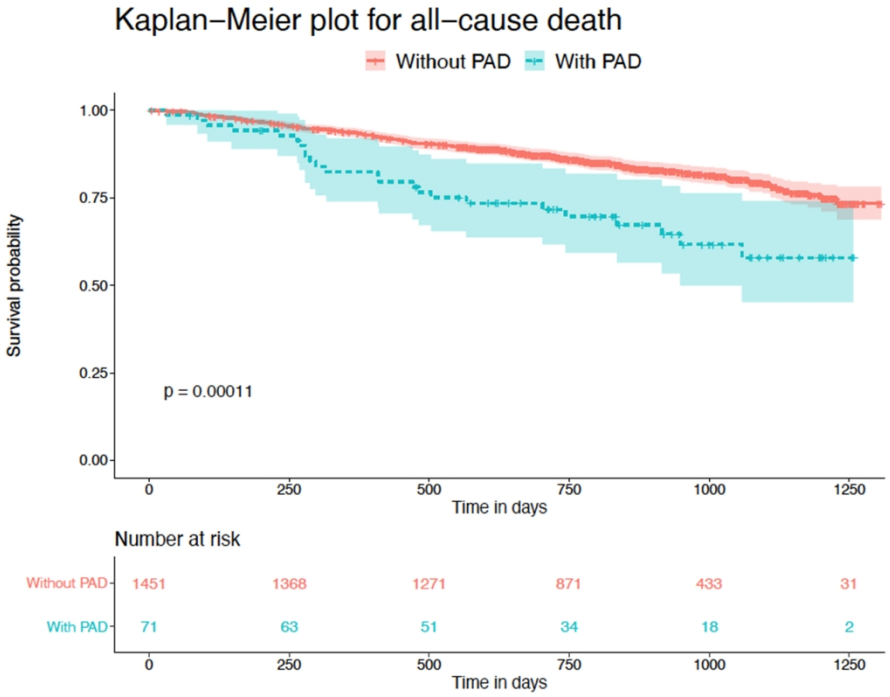


Figure 2. Kaplan-Meier plot for all-cause death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

254x190mm (300 x 300 DPI)

Figure 3.

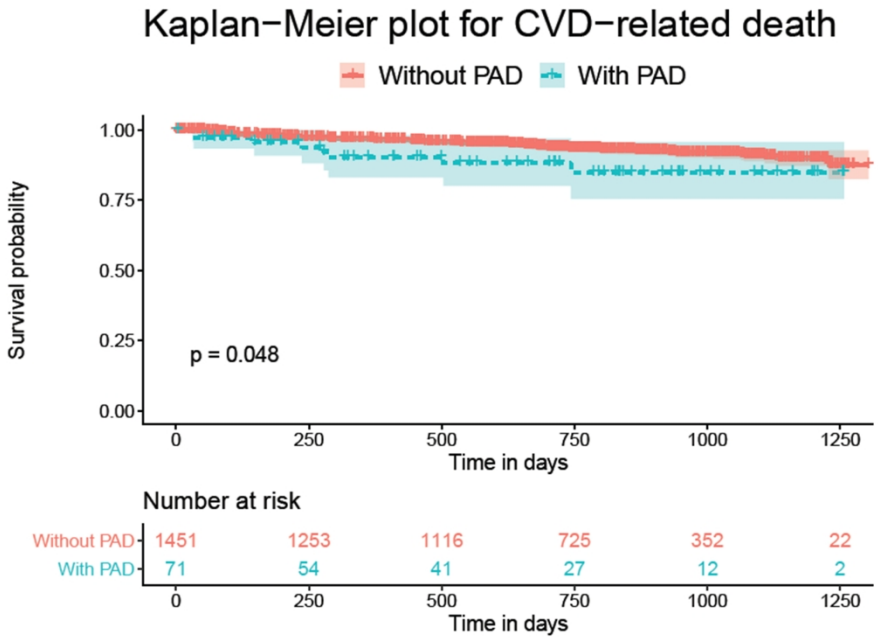


Figure 3. Kaplan-Meier plot for CVD-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease; CVD, cardiovascular disease.

254x190mm (300 x 300 DPI)

Figure 4.

Figure 4. Kaplan-Meier plot for infection-related death in patients (n = 1522) who started dialysis. PAD, peripheral artery disease.

254x190mm (300 x 300 DPI)

Figure 5.

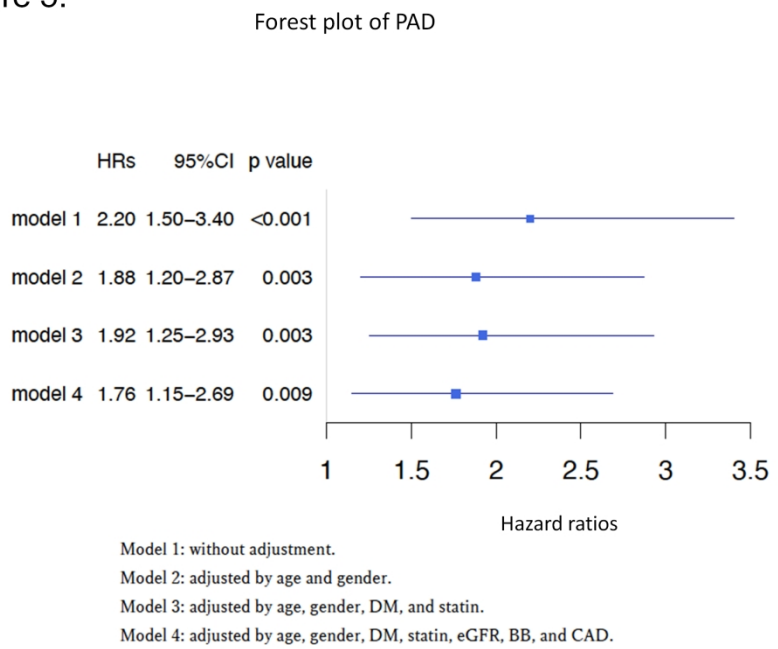


Figure 5. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

254x190mm (300 x 300 DPI)

Figure 6.

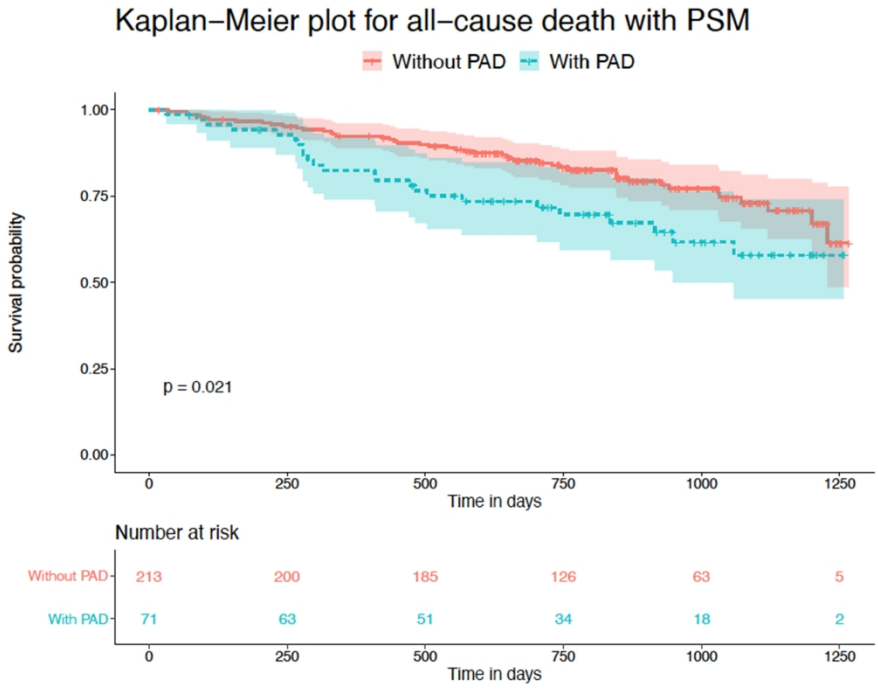


Figure 6. Kaplan-Meier plot for all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. PAD, peripheral artery disease; PSM, propensity score matching.

254x190mm (300 x 300 DPI)

Supplement material

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

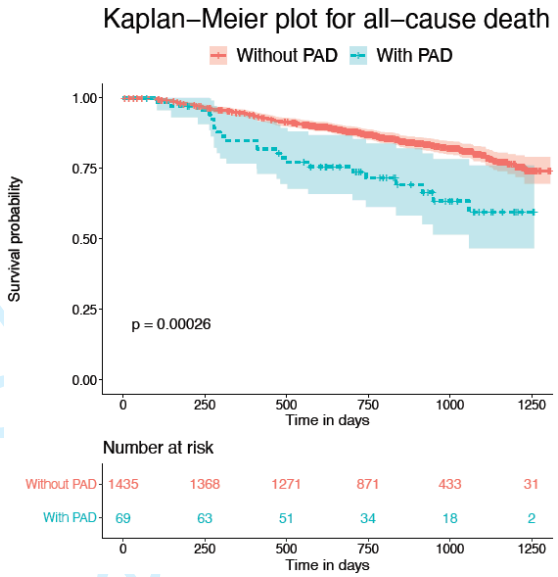
Hikaru Morooka,[1] Akihito Tanaka,[1] Daijo Inaguma[2], Shoichi Maruyama[3]

[1]Division of Nephrology, Nagoya University Hospital, Nagoya, Japan

[2] Division of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan

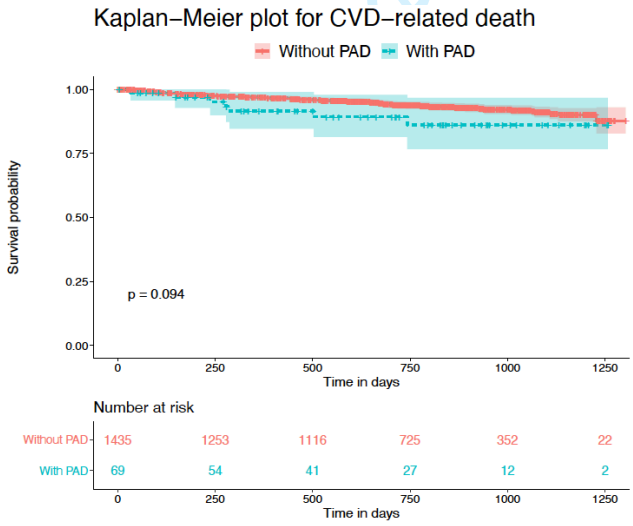
[3]Division of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Supplement material:



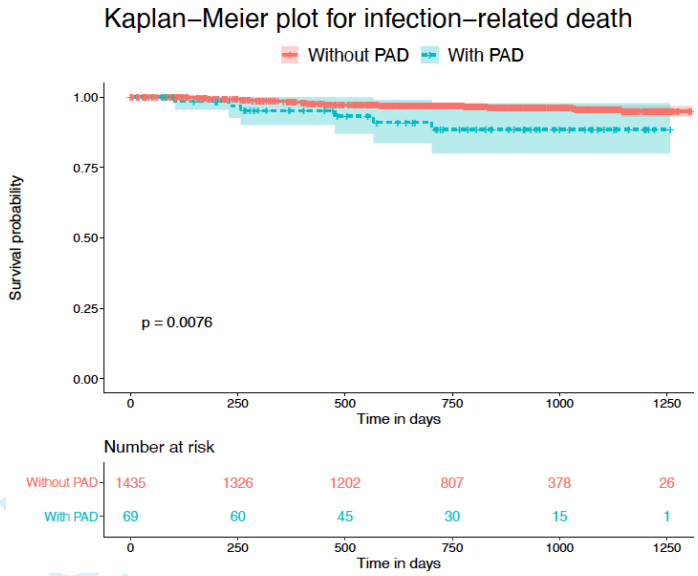
Supplemental figure 1:

The Kaplan-Meier plot for all-cause death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.



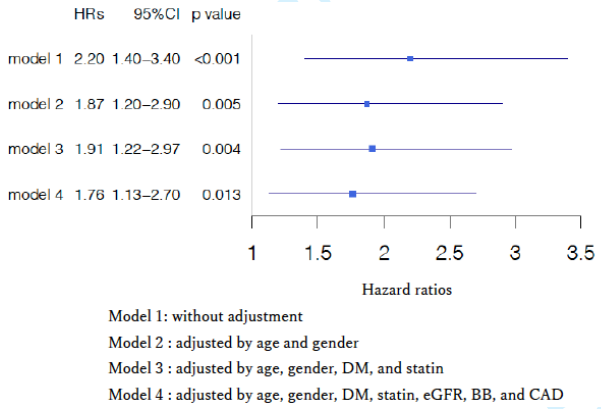
Supplemental figure 2:

The Kaplan-Meier plot for CVD-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease; CVD, cardiovascular disease.



Supplemental figure 3:

The Kaplan-Meier plot for infection-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.



Supplemental figure 4:

Hazard ratio of PAD for all-cause death in patients who survived longer than 3 months after the dialysis beginning (n = 1504). HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7, Figure 1
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Figure 1
		(b) Give reasons for non-participation at each stage	7, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 5
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042315.R2
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2020
Complete List of Authors:	Morooka, Hikaru; Nagoya University Hospital, Nephrology Tanaka, Akihito; Nagoya University Hospital, Nephrology Inaguma , D.; Fujita Health University, Nephrology Maruyama, Shoichi; Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Department of Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

Hikaru Morooka,[1] Akihito Tanaka,[1] Daijo Inaguma[2], Shoichi Maruyama[3]

[1]Division of Nephrology, Nagoya University Hospital, Nagoya, Japan

[2] Division of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan

[3]Division of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Corresponding author: Akihito Tanaka

Division of Nephrology,

Nagoya University Hospital

Tsurumaicho, 65, Showa Ward, Nagoya, Aichi, Japan

Tel: +81-52-741-2111

Fax: +81-52-744-2209

E-mail: tanaka17@med.nagoya-u.ac.jp

Word count: 3251.

ABSTRACT

Objectives: Patients with peripheral artery disease (PAD) are reported to have a poorer prognosis than those without PAD. PAD is sometimes found at dialysis initiation, but its influence on the prognosis in these patients has not been investigated. We aimed to compare the mortality between patients with PAD at the time of dialysis initiation and those without PAD.

Design: We undertook an observational prospective multicenter study of patients starting dialysis therapy. Data were collected on patients' sex, age, presence of PAD, medication, past medical history, and clinical and laboratory data.

Setting: Seventeen centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis.

Participants: A total of 1524 patients with chronic kidney disease who started dialysis from October 2011 to September 2013. The patients were followed up until March 2015. During this time, there were two patients lost to follow-up.

Primary and secondary outcome measures: The primary outcome was defined as all-cause death. The secondary outcomes were defined as each cause of death**.**

Results: The study included 1030 men and 492 women with a mean age of 67.50 ± 13.10 years. Of these, 71 had PAD, and 1451 did not. After a median follow-up of 814.5 days, 33.80 % of the former and 17.00 % of the latter group had died by March 2015 ($p = 0.001$). After adjusting for confounding factors, PAD at dialysis initiation remained an independent risk factor for mortality ($p < 0.01$).

Conclusions: Patients with PAD at the time of dialysis initiation had a poorer prognosis than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Key words: Chronic kidney diseases; Dialysis; Mortality; Peripheral artery disease

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This observational prospective multicenter study analyzed data in patients at the beginning of dialysis and for a median follow-up of 814.5 days.
- Our study had a high follow-up rate (only two patients lost to follow-up) and a well-defined population with comprehensive data at the start of dialysis.
- The number of patients with PAD at the initiation of dialysis was comparably small, and not all of them underwent other tests such as, contrast-enhanced computed tomography, magnetic resonance angiography, and peripheral angiography to confirm the diagnosis.

INTRODUCTION

The number of patients receiving dialysis therapy is increasing every year, and these patients have a high mortality risk from various causes, particularly cardiovascular diseases (CVD).[1, 2] End-stage kidney disease (ESKD) represents a considerable risk of atherosclerosis, and patients on dialysis tend to have further risk factors contributing to the rapid deterioration of CVD.[3] While CVD, including stroke, and coronary artery disease have been reported in more detail in patients on dialysis,[4-6] the problem of peripheral artery disease (PAD) in patients undergoing dialysis therapy has been less frequently addressed. With both aging and a growing number of diabetic patients on dialysis, the prevalence of PAD among these patients is likely to increase year by year.[7] PAD with distal lesions is more common in patients with ESKD, making the transarterial approach to the stenosis sometimes difficult.[8, 9] Furthermore, a vascular stenosis can promote peripheral ischemic skin ulcers or gangrene, leading to an intractable pathology. Thus, patients with PAD on dialysis therapy have a worse prognosis than those without PAD.[10] Consequently, there is an urgent need to clarify the relationships between PAD and mortality in patients on dialysis. Furthermore, to improve the prognosis of dialysis patients, it is crucial to understand the characteristics of those with high mortality risk.

The classic atherosclerosis risk factors, such as age, smoking, diabetes, hypertension, and hyperlipidemia, are common in patients with ESKD, but their chronic kidney disease (CKD) condition adds unique risk factors that promote PAD: chronic inflammation, hypoalbuminemia, and a pro-calcific state. PAD in ESKD patients markedly increases the possibility of myocardial ischemia and stroke, and is the main cause of limb loss and mortality, the rates of which are much higher than those in the general population.[10,11] Moreover, it has been pointed out that if patients with PAD develop critical limb ischemia, their overall survival is worse than that of patients with malignant tumors.[12] Hence, when considering the prognosis of patients receiving dialysis, the presence of PAD is important.

There are few recent reports on PAD in patients with ESKD at the time of dialysis initiation. Several studies have investigated patients receiving maintenance dialysis. In these studies, descriptive data included the prognosis of "only maintenance dialysis" patients.[10, 13-15] According to them, PAD had an overall prevalence of 18.2 %, and the patient survival rate was 28.6 % during 8.8 years in the PAD group. Moreover, since these studies focused on patients on maintenance dialysis, they mainly addressed PAD that occurred during dialysis. However, renal function in patients with CKD may decrease during the treatment of PAD. At other times, PAD is found when investigating the cause of renal function deterioration or when screening patients for their eligibility for a renal transplant. PAD at the time of dialysis initiation is a complex and clinically relevant problem.

In the present study, we compared PAD and non-PAD patients who had started dialysis therapy in the Aichi prefecture to identify the mortality associated with PAD in ESKD patients at the time of initiation of dialysis therapy.

PATIENTS AND METHODS

Patient registration and data collection

Data from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis [14, 16] were used in this prospective multicenter study. Patients who started dialysis between October 2011 and September 2013 at 17 Japanese institutions were eligible for participation. This study was approved by the Ethics Committee of the Institutional Review Board in Nagoya University (Approval number 1335), and all patients provided written informed consent.

First, we screened all patients with ESKD in whom dialysis was initiated. Only patients who became stable and were discharged or transferred from the hospital were included. Patients who were not discharged and died in the hospital were excluded (Figure 1). Data regarding patients' demographics, medical history, comorbidities, medications, and laboratory data

during the period of dialysis initiation were collected. PAD was clinically diagnosed based on symptoms, physical findings, and various examinations, but not all patients received angiography for diagnosis. After physicians carefully evaluated patients, we used the Fontaine classification for grading of severity. [17] The presence of PAD was defined as a Fontaine stage II or higher. Laboratory data were obtained immediately prior to the first dialysis session. Patients were followed by survey slips sent to the dialysis facilities until the end of March 2015.

Mortality

Patients were divided into one group with PAD and one group without PAD. The primary endpoint was all-cause mortality. Causes of death were recorded to the extent possible. The occurrence of death was investigated via survey slips sent to the dialysis facilities at the end of March 2015.

We compared the outcomes, hazard ratios (HRs) and logistic regression model between the two groups.

Statistics

Baseline characteristics were presented descriptively and compared between the two groups using the Student's *t*-test or χ^2-test. Survival was presented graphically using the Kaplan-Meier method and analyzed using uni- and multivariate Cox regression, and uni- and multivariate logistic regression model. HRs were calculated and presented graphically using forest plots. Odds ratios (ORs) were calculated and presented on a table. We used propensity score matching to account for differences in baseline characteristics between the two groups. The propensity score was calculated based on age, sex, presence of diabetes, medication (use of statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta

blockers, and antiplatelets), laboratory data (levels of phosphorus, hemoglobin, and estimated glomerular filtration rate), and history of coronary artery disease.

P-values of < 0.05 were considered to be statistically significant. We used the R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/) for all statistical analysis. For the propensity score matching, the R-package MatchIt (1:3 matching with the nearest neighbor) was used.[18] Missing data were not complemented, however the characteristics we used for propensity score matching were not missing. Moreover, we conducted the marginal structural Cox model between two groups after propensity score matching.

Patient and public involvement

Patients were not involved at any stage of the research for this study.

RESULTS

Baseline characteristics

Patients' baseline characteristics are shown in Table 1. The initial population included 1524 participants, of whom 1032 were men, and 492 were women. The mean age was 67.50 ± 13.10 years. Two patients were untraceable and lost to follow-up. Of the remaining 1522 patients, 71 (4.70%) had PAD, and 1451 did not. There were significant differences between patients with and without PAD with regard to comorbidities and drug use. Antiplatelet administration was significantly more frequent in those with PAD than in those without PAD. This may be because treatment for PAD includes antiplatelets. However, since other causes, such as myocardial infarction, can be the reason why these patients were on the antiplaltelet therapy. The prevalence of diabetes mellitus, coronary artery disease, and aortic dissection was significantly higher in those with than in those without PAD. Patients with PAD had significantly lower

ejection fractions than patients without PAD. The use of both beta-blockers and statins was significantly higher in patients with PAD than in those without PAD (beta-blockers: 34.00 % and 47.90 %, respectively, p = 0.024; statins: 39.40 % and 53.50 %, respectively, p = 0.024). The estimated glomerular filtration rate [19] was significantly higher in patients with PAD than in those without PAD (6.34 ± 1.83 mL/min per 1.7 m^2 and 5.40 ± 2.23 mL/min per 1.7m^2, respectively, p = 0.001). The median follow-up was 814.5 days (interquartile range 645-1037).

Mortality

During the follow-up period, 271 patients died from various causes, including cardiovascular events (102 patients, 37.6 %), infectious disease (56 patients, 20.7 %), cancer (45 patients, 16.6 %), and other causes. The PAD group had a significantly higher mortality rate of 33.80 % than the group without PAD with 17.00 % (p = 0.001; Table 1). Figure 2 (a) shows the Kaplan-Meier plot for all-cause mortality in patients with and without PAD. Figure 2 (b) shows the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p = 0.048). Figure 2 (c) shows the Kaplan-Meier plot for infection-related mortality in patients with and without PAD. The former group had a significantly higher mortality rate than the latter group (p = 0.011). Figure 3 shows the forest plot for the HRs of PAD for all-cause death with adjustment for confounding factors. PAD was an independent risk factor for death (HR, 1.76; 95 % confidence interval, 1.15–2.69; p = 0.009). As sensitivity analyses, we conducted the same analyses on patients, who survived longer than 3 months after the observation beginning. The results resembled the former ones (Supplemental figure 1, 2, 3), except the Kaplan-Meier plot for CVD-related mortality in patients with and without PAD (p = 0.094; Supplemental figure 4).

Propensity score-matched comparison between patients with and without PAD

The baseline and clinical characteristics in Table 1 showed significant differences between patients in the group with and without PAD, suggesting that there was a possibility of bias. Table 1 shows the baseline characteristics of the propensity score-matched patients with (n=71) and without PAD (n=213).

Table 1. Baseline and clinical characteristics and outcomes of patients starting dialysis (n = 1522) and propensity-score matched patients starting dialysis (n = 284)

	Without propensity-score matched (n = 1522)			With propensity-score matched (n = 284)		
	Patients without PAD (n = 1451)	Patients with PAD (n= 71)	P value	Patients without PAD (n = 213)	Patients with PAD (n = 71)	P value
Female (%)	33.10	16.90	0.007	15.00	16.90	0.850
Age (years) (mean (SD))	67.40 (13.10)	69.90 (12.10)	0.106	69.10 (12.20)	69.90 (12.10)	0.607
Past history						
Diabetes (%)	50.20	67.60	0.006	67.10	67.60	1.000
CAD (%)	15.90	36.60	< 0.001	40.40	36.60	0.674
PCI (%)	9.60	21.10	0.003	26.80	21.10	0.431
CABG (%)	3.80	14.10	< 0.001	9.90	14.10	0.442
Aortic dissection (%)	5.00	15.50	< 0.001	7.00	15.50	0.057
Admission of HF (%)	19.40	42.30	< 0.001	29.10	42.30	0.057
Stroke (%)	9.10	7.00	0.704	14.10	7.00	0.175
Cause of CKD			0.294			0.091
Diabetes (%)	42.50	59.20		58.70	59.20	

Nephrosclerosis (%)	25.30	25.40		25.40	25.40	
CGN (%)	15.60	4.20		8.50	4.20	
Others, unknown (%)	4.30	4.20		2.30	4.20	
Vital data						
Pre-dialysis SBP (mmHg) (mean (SD))	151.10 (25.90)	151.70 (29.50)	0.843	151.80 (28.30)	151.70 (29.50)	0.977
Cardiac ultrasonography						
EF (%) (mean (SD))	60.90 (12.20)	55.80 (13.70)	0.001	59.80 (13.80)	55.80 (13.70)	0.049
Chest X-ray						
CTR (%) (mean (SD))	55.20 (7.20)	55.20 (7.10)	0.973	55.30 (6.80)	55.20 (7.10)	0.885
Administration						
ARB or ACEI (%)	60.60	56.30	0.554	59.20	56.30	0.781
BB (%)	34.00	47.90	0.024	49.30	47.90	0.945
Statin (%)	39.40	53.50	0.024	58.70	53.50	0.533
VDRA (%)	26.90	29.60	0.726	27.20	29.60	0.819
Antiplatelets (%)	28.90	56.30	< 0.001	58.20	56.30	0.890
ESA (%)	85.80	87.30	0.861	89.70	87.30	0.742
Laboratory data						
WBC (/uL) (mean (SD))	6729.88 (3130.80)	7206.62 (3581.54)	0.214	6704.76 (2722.41)	7206.62 (3581.54)	0.217
Hb (g/dL) (mean (SD))	9.37 (1.55)	9.40 (1.45)	0.887	9.62 (1.43)	9.40 (1.45)	0.275
Plt (10 000/uL) (mean (SD))	18.24 (7.62)	18.17 (8.19)	0.943	17.90 (7.39)	18.17 (8.19)	0.796

Alb (g/dL) (mean (SD))	3.21 (0.59)	3.02 (0.62)	0.010	3.20 (0.60)	3.02 (0.62)	0.032
BUN (mg/dL) (mean (SD))	92.02 (30.69)	86.68 (24.84)	0.149	87.14 (27.58)	86.68 (24.84)	0.901
Cr (mg/dL) (mean (SD))	9.03 (3.24)	7.74 (2.22)	0.001	8.47 (2.82)	7.74 (2.22)	0.049
eGFR (mL/min/1.73m^2) (mean (SD))	5.40 (2.23)	6.34 (1.83)	0.001	6.05 (2.47)	6.34 (1.83)	0.368
Na (mEq/L) (mean (SD))	137.88 (4.41)	137.93 (3.91)	0.933	138.36 (4.56)	137.93 (3.91)	0.475
K (mEq/L) (mean (SD))	4.56 (0.84)	4.43 (0.81)	0.194	4.51 (0.83)	4.43 (0.81)	0.492
Adjusted Ca (mg/dL) (mean (SD))	8.59 (1.06)	9.06 (0.93)	< 0.001	8.71 (0.96)	9.06 (0.93)	0.007
P (mg/dL) (mean (SD))	6.40 (1.89)	5.76 (1.56)	0.005	5.96 (1.63)	5.76 (1.56)	0.372
Mg (mg/dL) (mean (SD))	2.15 (0.49)	2.17 (0.44)	0.826	2.22 (0.46)	2.17 (0.44)	0.497
UA (mg/dL) (mean (SD))	8.80 (2.44)	8.64 (2.27)	0.582	8.75 (2.49)	8.64 (2.27)	0.731
LDL C (mg/dL) (mean (SD))	89.97 (34.25)	87.08 (37.14)	0.525	87.07 (32.01)	87.08 (37.14)	0.999
CRP (mg/dL) (mean (SD))	1.82 (4.14)	2.39 (4.68)	0.271	1.61 (3.30)	2.39 (4.68)	0.137
β2MG (ng/dL) (mean (SD))	19.32 (5.78)	17.33 (5.05)	0.027	17.95 (5.04)	17.33 (5.05)	0.497
TSAT (%) (mean (SD))	27.16 (16.60)	25.44 (17.95)	0.438	25.41 (14.74)	25.44 (17.95)	0.992
Ferritin (ng/dL) (mean (SD))	222.28 (1009.80)	226.65 (395.74)	0.972	171.44 (208.99)	226.65 (395.74)	0.153
Outcome						
Infection-related death (%)	3.40	8.50	0.062	3.80	8.50	0.206
CVD-related death (%)	6.60	11.60	0.167	8.20	11.60	0.537
All-cause death (%)	17.00	33.80	0.001	21.60	33.80	0.056

ACEI; angiotensin-converting enzyme inhibitor. Adjusted Ca; adjusted calcium. Alb; albumin. ARB; angiotensin receptor blocker. BB; beta blocker. BUN; blood urea nitrogen. β 2MG; beta-2 microglobulin. Ca; calcium. CABG; coronary artery bypass grafting. CAD; coronary artery disease. CGN; chronic glomerulonephritis. CKD; chronic kidney disease. Cr; creatinine. CRP; C-reactive protein. CTR; cardiothoracic ratio. CVD; cardiovascular disease. EF; ejection fraction. eGFR; estimated glomerular filtration rate. ESA; erythropoietin stimulating agent. Hb; hemoglobin. HF; heart failure. K; potassium. LDL-C; low-density lipoprotein cholesterol. Mg; magnesium. Na; sodium. P; phosphate. PAD; peripheral arterial disease. PCI; percutaneous coronary intervention. Plt; platelet. SBP; systolic blood pressure. SD; standard deviation. TSAT; transferrin saturation. UA; uric acid. VDRA; Vitamin D receptor agonist. WBC; white blood cells.

Figure 2 (d) shows the Kaplan-Meier plot for all-cause death in matched patients with and without PAD. Patients with PAD showed a significantly worse prognosis than those without. For CVD-related and infection-related death, respectively, in matched patients with and without PAD with no significant differences between the groups ($p = 0.300$, $p = 0.069$). In logistic regression analysis including propensity score into multivariable factors, patients with PAD had significantly worse prognosis than patients without PAD (Table 2). Supplemental Table 1 shows results of the marginal structural Cox model. In all models, PAD was an independent risk factor even after propensity score matching (HRs > 2.20, $p < 0.01$).

Table 2. Odds ratios of the mortality of the patients (n = 1522)

	Odds Ratio	95% CI	p value
Model 1	2.49	1.49 - 4.15	< 0.001
Model 2	2.00	1.18 - 3.38	0.010
Model 3	2.12	1.24 - 3.61	0.006
Model 4	1.93	1.12 - 3.30	0.017

Model 1: PAD

Model 2: PAD + propensity score

Model 3: PAD + propensity score + pre SBP

Model 4: PAD + propensity score + pre SBP + adjusted Calcium

CI; confidence interval. PAD; peripheral artery disease. SBP; systolic blood pressure

DISCUSSION

Our study showed that patients with PAD at the time of dialysis initiation had a significantly higher mortality than patients without PAD. This higher risk should be considered in the treatment and monitoring of these patients.

A previous study suggested that the prevalence of PAD in patients with ESKD reached almost 20 %. [15] In our cohort, the prevalence of PAD was much lower, most likely because our patients started dialysis, whereas the patients in the literature where on maintenance dialysis. This might reflect a deterioration of peripheral atherosclerosis with longer duration of dialysis. Another study suggested that the chronic uremic state is associated with systemic inflammation in dialysis patients, leading to hypoalbuminemia and an increased risk of PAD. [20] Hence, our results are remarkable because we showed the prevalence of PAD at the time of dialysis initiation, while past studies reported on PAD during maintenance dialysis. Furthermore, patients with PAD in our study more frequently had a decreased ejection fraction and decreased albumin and increased adjusted calcium levels than those without PAD, even after propensity score matching. We cannot exclude the possibility of other factors associated with PAD that were not corrected even after our propensity score matching. This implies that PAD is one symptom of a systemic atherosclerotic disease that affects not only the peripheral but also coronary arteries. When seeing patients with myocardial infarction or low cardiac systolic function, it is recommended to suspect that they have PAD. [7]

In this study, patients with PAD at the time of dialysis initiation had a worse prognosis than patients without PAD. Patients with PAD suffered more frequently from CVD and infectious diseases. After propensity score matching, all-cause mortality still indicated a similar result. As our propensity score included a history of coronary artery disease, we could not show a significant difference between patients with and without PAD regarding this aspect. We assume that the number of patients with PAD was too small to demonstrate a significant

difference in infection-related deaths between patients with and without PAD. However, these results support that atherosclerosis is likely to occur not only in the coronary but also in the peripheral arteries in patients with ESKD. PAD is a systemic disease, which can negatively affect patients' prognosis. Based on our findings, it is critical to detect patients with PAD at the time of dialysis initiation.

Our results should be interpreted within the limitations of our study. Firstly, as this was an observational study, there is an inevitable selection bias in our patients with ESKD and PAD. Secondly, the number of patients with PAD was small, and the number of patients who received ankle brachial index (ABI) is not available. Because we did not examine ABI for all patients, we were not able to diagnose asymptomatic patients or those who did not describe their symptoms seen in PAD. ABI is a frequently used examination for PAD diagnosis and the lack of this result is important. Furthermore, how many patients underwent other diagnostic tests, such as contrast-enhanced computed tomography, magnetic resonance angiography, and peripheral angiography, and the results of these tests were unavailable. Hence, the statistical power of our results may be low. Furthermore, we did not include patients with Fontaine stage I into the PAD group. However, our study included a well-defined population as a strength.

CONCLUSION

Patients with PAD at the time of dialysis initiation showed higher rates of mortality than patients without PAD. Therefore, the presence of PAD in patients starting dialysis should be considered in their monitoring and follow-up.

Acknowledgments

We acknowledge the support of the following members of the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) for this study: Hirofumi Tamai (Anjo Kosei

Hospital), Tomohiko Naruse (Kasugai Municipal Hospital), Kei Kurata (Tosei General Hospital), Hideto Oishi (Komaki City Hospital), Isao Aoyama (Japan Community Healthcare Organization Chukyo Hospital), Hiroshi Ogawa (Shinseikai Daiichi Hospital), Hiroko Kushimoto (Nishichita General Hospital), Hideaki Shimizu (Chubu-Rosai Hospital), Junichiro Yamamoto (Tsushima City Hospital), Hisashi Kurata (Toyota Kosei Hospital), Taishi Yamakawa (Toyohashi Municipal Hospital), Takaaki Yaomura (Nagoya Medical Center), Hirotake Kasuga (Nagoya Kyouritsu Hospital), Shizunori Ichida (Japanese Red Cross Nagoya Daiichi Hospital), Hibiki Shinjo (Japanese Red Cross Nagoya Daini Hospital), Shigehisa Koide (Fujita Health University Hospital), and Yukio Yuzawa (Fujita Health University Hospital).

Individual author contributions

DI conceived and designed the study. DI developed the bespoke dataset. AT accessed the dataset, contributed to data analysis and interpretation, and provided feedback on the article. HM performed the data analysis and interpretation, wrote the first draft of the article, and subsequent revisions. SM contributed to study design, provided feedback on the article, and approved the submitted version. All authors have approved the final version for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

None declared.

Data availability statement

No additional data are available.

Patient and public involvement

No patients were involved.

REFERENCES

1. Sato T, Sakurai H, Okubo K, et al. Current state of dialysis treatment and vascular access management in Japan. *J Vasc Access* 2019;20:10–14. doi: 10.1177/1129729819838183.

2. Masakane I, Nakai S, Ogata S, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). *Ther Apher Dial* 2015;19:540–74. doi: 10.1111/1744-9987.12378.

3. Cozzolino M, Galassi A, Pivari F, et al. The cardiovascular burden in end-stage renal disease. *Contrib Nephrol* 2017;191:44–57. doi: 10.1159/000479250.

4. Cozzolino M, Mangano M, Stucchi A, et al. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018;33:iii28–iii34. doi: 10.1093/ndt/gfy174.

5. U.S. Renal Data System. Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2009.

6. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003;64:603–9. doi: 10.1046/j.1523-1755.2003.00101.x.

7. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: Clinical synergy to improve outcomes. *Adv Chronic Kidney Dis* 2014;21:460–71. doi: 10.1053/j.ackd.2014.07.005.

8. Kumada Y, Aoyama T, Ishii H, et al. Long-term outcome of percutaneous transluminal angioplasty in chronic haemodialysis patients with peripheral artery disease. *Nephrol Dial Transplant* 2007;23:3996–4001. doi: 10.1093/ndt/gfn378.

9. Graziani L, Silvestro A, Bertone V, et al. Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. *Nephrol Dial Transplant* 2007;22:1144–9. doi: 10.1093/ndt/gfl764.

10. Otsubo S, Kitamura M, Wakaume T, et al. Association of peripheral artery disease and long-term mortality in hemodialysis patients. *Int Urol Nephrol* 2012:44:569–73. doi: 10.1007/s11255-010-9883-8.

11. Liew YP, Bartholomew JR, Demirjian S, et al. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. *Clin J Am Soc Nephrol* 2008;3:1084–9. doi: 10.2215/CJN.04411007.

12. O'Hare AM, Feinglass J, Sidawy AN, et al. Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 2003; 14:1287–95. doi: 10.1097/01.asn.0000061776.60146.02.

13. Liu JH, Chen JY, Lin SY, et al. Comparing survival between peritoneal dialysis and hemodialysis with subclinical peripheral artery disease: a 6-year follow up. *Int J Med Sci* 2013:10:434–40. doi: 10.7150/ijms.5091.

14. Hishida M, Tamai H, Morinaga T, et al. Aichi cohort study of the prognosis in patients newly initiated into dialysis (AICOPP): baseline characteristics and trends observed in diabetic nephropathy. *Clin Exp Nephrol* 2016;20:795–807. doi: 10.1007/s10157-015-1206-z.

15. Lee CC, Wu CJ, Chou LH, et al. Peripheral artery disease in peritoneal dialysis and hemodialysis patients: single-center retrospective study in Taiwan. *BMC Nephrol* 2012:13:100. doi: 10.1186/1471-2369-13-100.

16. Tanaka A, Inaguma D, Shinjo H, et al. Presence of atrial fibrillation at the time of dialysis initiation is associated with mortality and cardiovascular events. *Nephron* 2016;132:86–92. doi: 10.1159/000443314.

17. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders [in German]. *Helv Chir Acta* 1954;21:499–533.

18. Ho DE, Imai K, King G, et al. MatchIt: Nonparametric preprocessing for parametric causal inference. *J Stat Soft* 2011:42:1–28.

19. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92. doi: 10.1053/j.ajkd.2008.12.034.

20. Cooper BA, Penne EL, Bartlett LH, et al. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kidney Dis* 2004:43:61–6. doi: 10.1053/j.ajkd.2003.08.045.

Figure legends

Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

Figure 2. Kaplan-Meier plots. (a) all-cause death in patients (n = 1522) who started dialysis. (b) CVD-related death in patients (n = 1522) who started dialysis. (c) infection-related death in patients (n = 1522) who started dialysis. (d) all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. CVD, cardiovascular disease; PAD, peripheral artery disease; PSM, propensity score matching.

Figure 3. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

Supplement figure legends

Supplemental figure 1:

The Kaplan-Meier plot for all-cause death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.

Supplemental figure 2:

The Kaplan-Meier plot for infection-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.

Supplemental figure 3:

Hazard ratio of PAD for all-cause death in patients who survived longer than 3 months after the dialysis beginning (n = 1504). HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

Supplemental figure 4:

The Kaplan-Meier plot for CVD-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease; CVD, cardiovascular disease.

Figure 1.

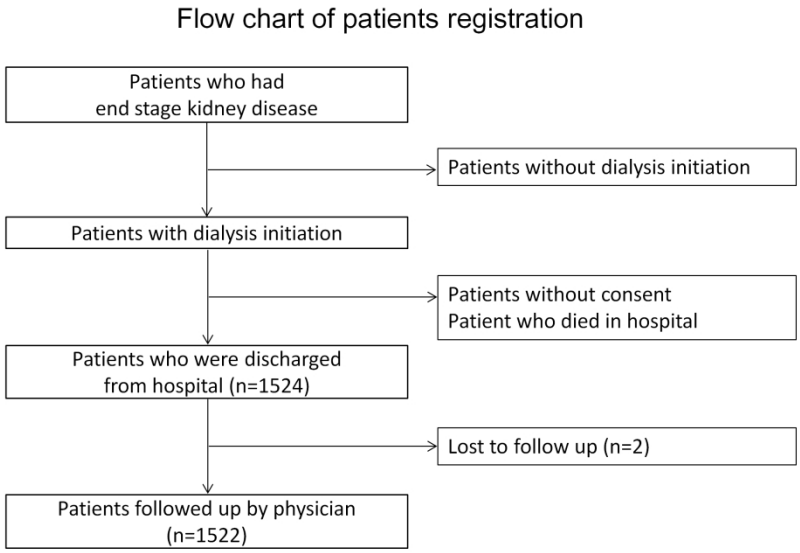


Figure 1. Flow chart of patients with end-stage kidney disease through this observational study. Only patients who became stable and were discharged from the hospital with consent were included. Patients who were not discharged and died in the hospital were excluded.

254x190mm (300 x 300 DPI)

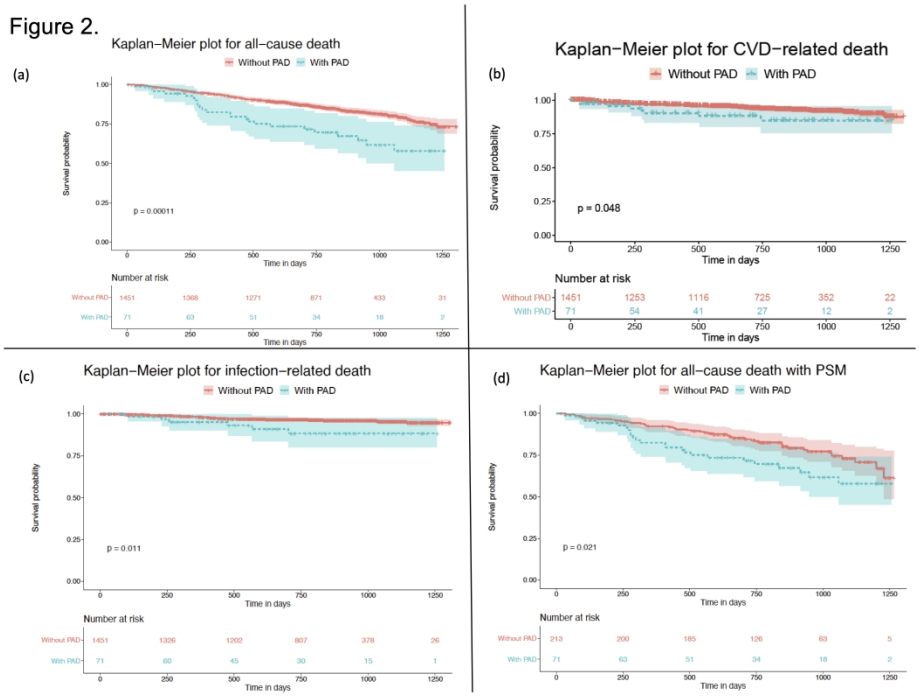


Figure 2. Kaplan-Meier plots. (a) all-cause death in patients (n = 1522) who started dialysis. (b) CVD-related death in patients (n = 1522) who started dialysis. (c) infection-related death in patients (n = 1522) who started dialysis. (d) all-cause death in propensity score-matched patients (n = 284) with and without PAD who started dialysis. CVD, cardiovascular disease; PAD, peripheral artery disease; PSM, propensity score matching.

296x209mm (300 x 300 DPI)

Figure 3.

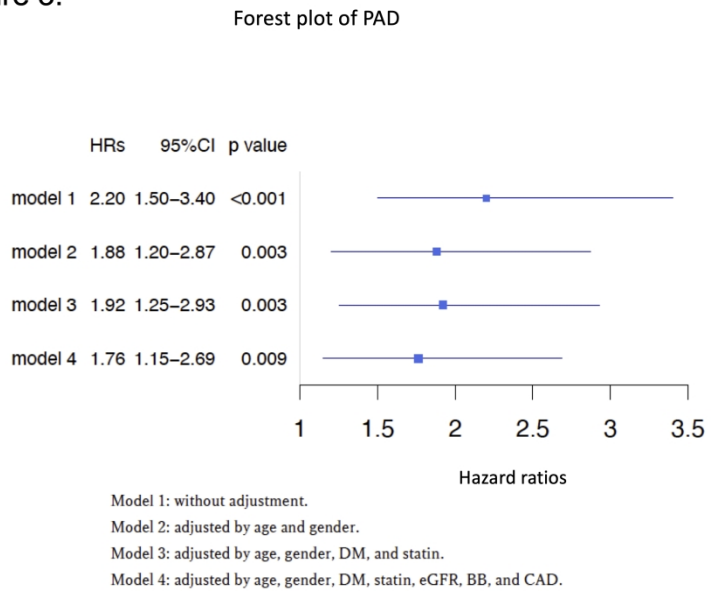


Figure 3. Hazard ratio of PAD for all-cause death. HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.

296x209mm (300 x 300 DPI)

Supplement material

Peripheral artery disease at the time of dialysis initiation and mortality: a prospective observational multicenter study

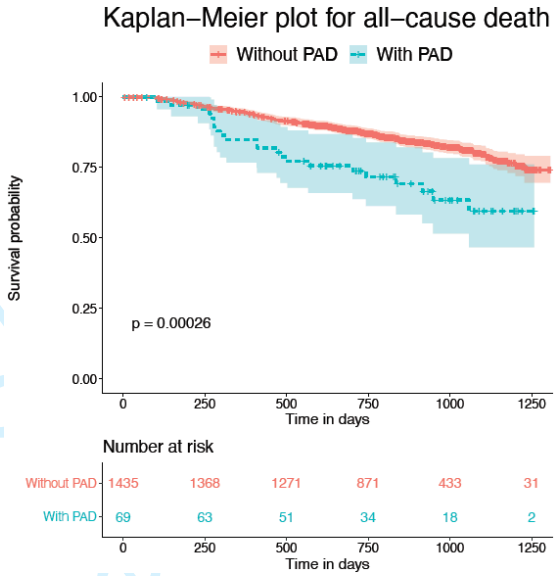
Hikaru Morooka,[1] Akihito Tanaka,[1] Daijo Inaguma[2], Shoichi Maruyama[3]

[1]Division of Nephrology, Nagoya University Hospital, Nagoya, Japan

[2] Division of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan

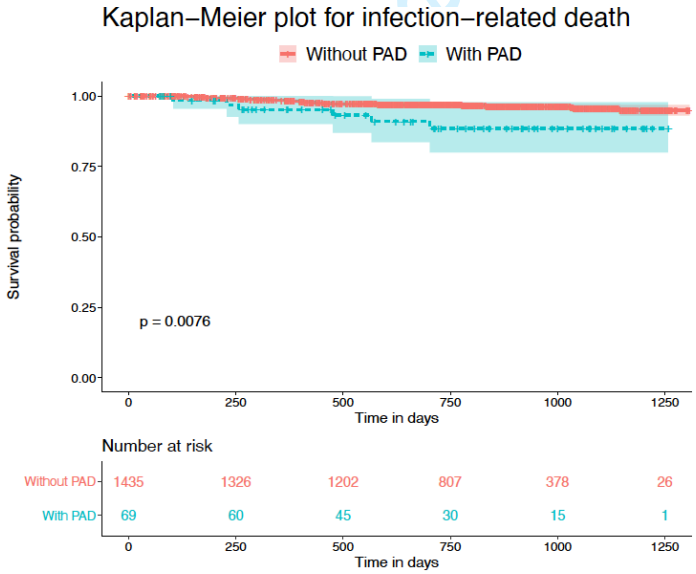
[3]Division of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Supplement material:



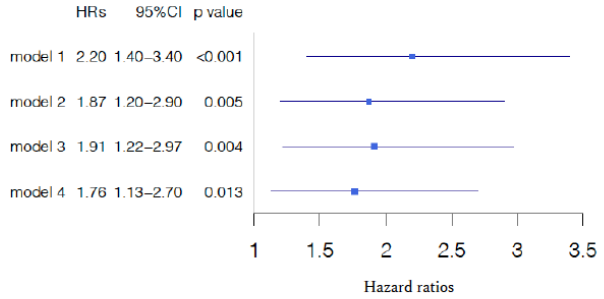
Supplemental figure 1:

The Kaplan-Meier plot for all-cause death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.



Supplemental figure 2:

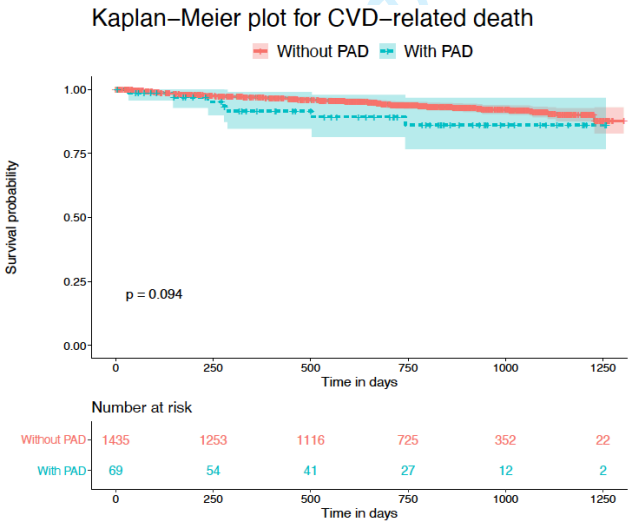
The Kaplan-Meier plot for infection-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease.



Model 1: without adjustment
Model 2 : adjusted by age and gender
Model 3 : adjusted by age, gender, DM, and statin
Model 4 : adjusted by age, gender, DM, statin, eGFR, BB, and CAD

Supplemental figure 3:

Hazard ratio of PAD for all-cause death in patients who survived longer than 3 months after the dialysis beginning (n = 1504). HR, hazard ratio; PAD, peripheral artery disease. CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BB, beta-blocker; CAD, coronary artery disease.



Supplemental figure 4:

The Kaplan-Meier plot for CVD-related death for patients who survived longer than 3 months after the dialysis beginning (n = 1504). PAD, peripheral artery disease; CVD, cardiovascular disease.

Supplemental table 1: Hazard ratios of the mortality of the patients (n = 1522)

	HR (95% CI)	P value
Model 1	2.44 (1.32 – 4.51)	0.004
Model 2	2.62 (1.43 – 4.80)	0.002
Model 3	2.29 (1.27 – 4.12)	0.006

Model 1: PAD

Model 2: PAD + pre SBP

Model 3: PAD + pre SBP + adjusted Calcium

CI; confidence interval. PAD; peripheral artery disease. SBP; systolic blood pressure

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7, Figure 1
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Figure 1
		(b) Give reasons for non-participation at each stage	7, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 5
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.